

The Development Of A One-Pot 1,4- Addition/Nitro-Mannich Reaction



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I, Matthew Robert Mills confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Date.....

Abstract

The introduction of this thesis reviews the three areas of importance to the research carried out. These are the nitro-Mannich reaction, the conjugate addition of nucleophiles to nitro-alkenes and the diastereoselectivity of electrophilic additions to substrates bearing an α -stereocentre.

The Results and Discussion details the research carried out into the development of a one-pot 1,4-addition/nitro-Mannich reaction. Initially the research focused on triggering the reaction using a cyanide nucleophile. Three cyanide sources were investigated, trimethylsilylcyanide, potassium ferrous cyanide and acetone cyanohydrin. Although the desired one-pot reaction was not achieved using any of these reagents, a new method for the addition of cyanide to nitro-alkenes was successfully developed, and the use of these unusual but highly versatile synthetic building blocks was briefly demonstrated.

More success was achieved with alkyl nucleophiles from dialkylzinc reagents. A one-pot 1,4-addition/nitro-Mannich sequence was discovered and optimised using diethylzinc. During the optimisation it was realised that the diastereoselectivity of the reaction was tuneable by the choice of solvent, using THF as the solvent provides the *syn/anti*-diastereoisomer as the major product, whilst reactions in Et₂O provide the *syn/syn*-diastereoisomer as the major product. The reaction scope was explored, and the reaction was rendered asymmetric *via* the employment of chiral additives. The reaction scope was determined to be very general, providing high levels of relative and absolute control across three contiguous stereocentres for a wide range of nitro alkenes and imines, and was also applicable to dimethylzinc and diphenylzinc. Finally a model was proposed for the resulting, solvent dependent stereochemistry.

Conclusions regarding the research carried out are presented, along with suggested future studies to be undertaken. These include reactions to further probe the mechanism and stereochemical model, as well as to increase the utility of the reaction further. The experimental section provides procedures and data for all novel compounds, X-ray crystallographic data and a comprehensive list of references.

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Finally I'd like to thank my friends and family who are always there on those (rare) occurrences when I wanted to celebrate or (more frequently) drown those sorrows. And of course I wouldn't dare forget my wife, Catherine, whose constant nagging kept me in the lab night and day (only joking). Your constant support has kept me going all these years, and hopefully for many more to come.

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Chapter 1:

Introduction

Introduction

1.1 Overview

The aim of this introduction is to briefly review the literature of the three key areas of research relevant to the results discussed in the Results and Discussion section. The first area to be discussed will be the key reaction of this thesis, the nitro-Mannich reaction. The history of this reaction spans over 100 years, yet there are only around 100 publications in this field, with the vast majority coming in the 21st century. The review will briefly cover the literature from conception to present day “state of the art.” The second area of concern is the addition of nucleophiles to nitro-alkenes. Nitro-alkenes are heavily polarised by the electron-withdrawing nature of the nitro group, and this makes them ideal substrates for the 1,4-addition of nucleophiles. Section 1.3 will briefly discuss only a subset of the research carried out in this field, that of asymmetric additions of carbon based nucleophiles. The final section of the introduction will look at a number of models used to predict the stereochemical outcome of electrophilic additions on trigonal carbon adjacent to a stereocentre. Whilst similar models have existed for the related addition of nucleophiles to trigonal carbon adjacent to a stereocentre (most famously Cram and Felkin-Anh models), the electrophilic additions have received much less attention. There are, however, several systems which have been examined from a variety of view points, and these will be discussed. Finally, the models previously discussed will be attempted to be applied to the few literature examples of nitro-Mannich reactions with a nitronate bearing an α -stereocentre.

1.2 The Nitro-Mannich Reaction

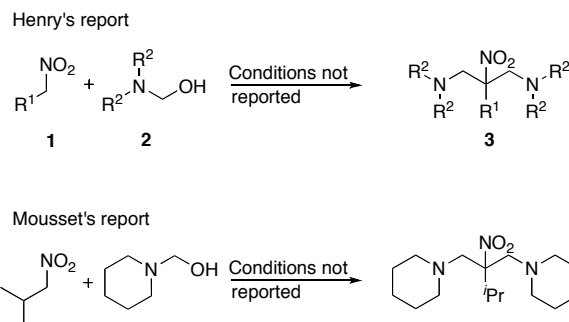
1.2.1 Overview

The additions of active C-H nucleophiles to C-heteroatom double bonds represent some of the most fundamental C-C bond forming processes in organic chemistry. Of these reactions, the aldol, nitroaldol (or Henry) and Mannich reactions have been studied extensively. The final member of this family of closely related reactions, the nitro-Mannich (or aza-Henry), is by far the least well researched. Recently, however, the reaction has received interest on account of the expedient access it allows to potent functional groups. In essence, the nitro-Mannich reaction requires the addition of a nitronate species to an imine electrophile, thus forming the central C-C bond of a β -nitroamine. Once formed, the versatile β -nitroamine functionality allows access to a wide range of synthetic targets through simple functional group interconversions. Early reports on the nitro-Mannich were of limited synthetic use, being unselective and often low yielding. In 1998, however, the first acyclic, stereoselective protocol was published,¹ and there now exist a large number of both enantio- and diastereoselective protocols using a wide range of catalysts, both organometallic and organo-catalytic in nature. The reaction has also been used in several target syntheses.

1.2.2 Discovery and Early Advances

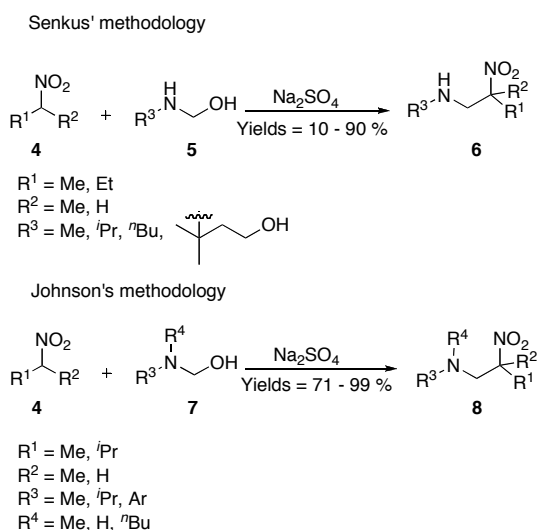
In 1896 Louis Henry reported the first nitroaldol reaction, later named the Henry reaction.² Just one year later he published the first example of the nitro-Mannich reaction, also known as the aza-Henry.³ Henry showed that nitro-alkanes **1** would add to hemi-aminals **2** to provide β -nitroamines **3** (**Scheme 1**). Although the exact conditions were not reported, presumably the reaction proceeds *via* the iminium formed from ejection of a molecule of water from **2**. Mousset reported

similar results a few years later, but again the exact conditions were not reported.⁴



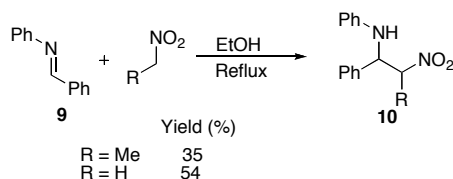
Scheme 1: The first reported nitro-Mannich reactions

Following these two reports no further research was published until the middle of the 20th century, when Senkus and Johnson published more detailed accounts of the previously reported conditions. Senkus demonstrated that a variety of β -nitroamines **6** could be synthesised from the addition of primary and secondary nitroalkanes **4** to hemiaminal **5** (**Scheme 2**).⁵ In an extension of this work Johnson showed that the reaction conditions would also tolerate aromatic substitution on hemiaminal **7**.⁶



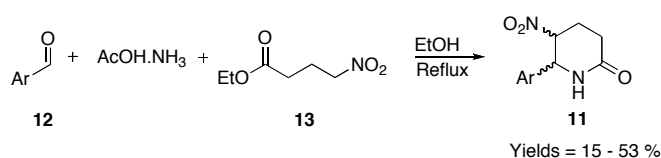
Scheme 2: Senkus' and Johnson's nitro-Mannich conditions

The next major development for the nitro-Mannich reaction came in 1950 when Hurd and Strong described the first nitro-Mannich reaction between a nitroalkane and a pre-formed imine.⁷ Imine **9**, derived from condensation of benzaldehyde and aniline, was coupled with both nitromethane and nitroethane by refluxing in ethanol, to provide the desired β -nitroamine **10**, although in only a moderate yield (**Scheme 3**).



Scheme 3: The first nitro-Mannich reaction between a nitro-alkane and a pre-formed imine

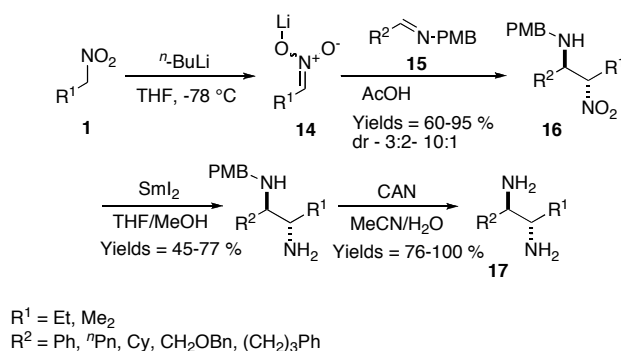
The last of the pre-1998 developments came in the form of a method for the synthesis of substituted piperidones **11**. Mühlstädt and Schulze demonstrated the coupling of benzaldehydes **12**, ammonium acetate and ethyl-4-nitrobutanoate **13** in the sequence of imine formation, nitro-Mannich reaction and subsequent lactamisation of the β -nitroamine (**Scheme 4**).⁸ The report does not mention whether any relative stereochemistry was observed, and the yields are only moderate (15-53 %); however, the following year Jain *et al.*⁹ published a similar procedure, but with the additional benefit of slightly improved yields (up to 98 %), confirmation of *trans*- stereochemistry (*via* ^1H NMR analysis) and also a single example of the use of phenethylammonium acetate. Recently Dixon *et al.* have developed an extended piece of methodology,¹⁰ using methyl-3-nitropropanoate as the nitroalkane (see section 1.2.8).



Scheme 4: The synthesis of piperidones *via* a nitro-Mannich/lactamisation cascade

1.2.3 Non-Catalytic Coupling

The previously mentioned reports of the early and mid 20th century are in one way or another of limited use in terms of synthetic practicalities. There is little consistency in yield, and little to no selectivity in terms of both absolute and relative stereocontrol, especially in acyclic cases. It was not until over 100 years after the initial report that synthetically useful protocols were developed. The following section will detail the key reports that allowed for the advancement of the nitro-Mannich to the valuable reaction it is today. The first of these was the work of the Anderson group, who published the first acyclic diastereoselective nitro-Mannich reaction between a pre-formed imine and a metal nitronate in 1998.¹ The direct addition of lithium nitronate **14** (accessed from deprotonation of nitroalkane **1**) to *para*-methoxybenzyl (PMB) protected aldimines **15** in the presence of a Brønsted acid provided *anti*- β -nitroamines **16** in excellent yields and diastereoselectivities. Unfortunately the products **16** proved to be unstable to purification, but a two-step reduction/deprotection strategy (again high yielding) allowed access to the synthetically useful vicinal diamine **17** (Scheme 5).



Scheme 5: The first acyclic diastereoselective nitro-Mannich reaction

In a later extension to this work, Anderson *et al.* were able to demonstrate a greater level of diastereo-control through the use of different protecting groups on the imine.¹¹ Encouraged by Jørgensen's report on the use of α -imino ester **18** in the nitro-Mannich reaction,¹² imines of the type depicted in **Figure 1** were explored. Jørgensen rationalises the high levels of stereoselectivity observed in his work to dual co-ordination of the imine to the copper centre, through both the imine nitrogen and the esters carbonyl oxygen (**Scheme 10**). The major drawback of this methodology is the requirement of the ester group, thus limiting the scope to a single imine **18**.

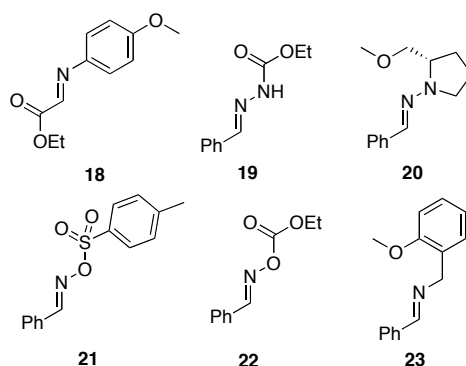
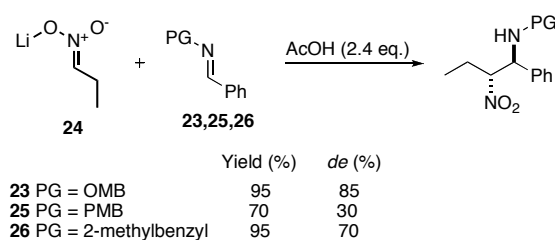


Figure 1: Imines investigated by the Jørgensen (**18**) and the Anderson research groups (**19-23**)

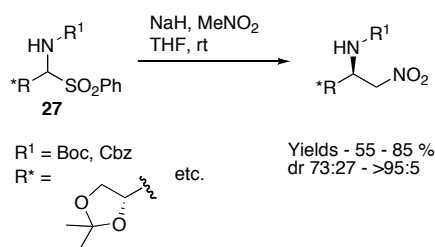
As can be seen from **Figure 1**, the imines **18-23** are capable of bidentate co-ordination to a metal centre. The advantage to those of the type **19-23** lies in the second co-ordination point lying within the nitrogen-protecting group rather than in the carbon substituent, allowing for much greater substrate scope. Although imines **19-22** were found to be inactive with respect to the nitro-Mannich reaction, imine **23** was active, and provided the expected increase in selectivity. The inactivity of imines **19-22** could be attributed to either the presence of additional heteroatoms reducing the electrophilicity of the imine, or an alternate co-ordination mode to the Lewis acid not involving the imine nitrogen, thus rendering the complex inactive. Control experiments coupling the lithium

nitronate of nitropropane **24** with imines containing further protecting groups (*para*-methoxybenzyl **25** and 2-methylbenzyl **26**) suggest that the reason for the enhanced selectivity is due to both steric and electronic effects (**Scheme 6**). The group also demonstrated that a similar level of diastereoselectivity was displayed when a catalytic amount of a Lewis acid (Cu (II), Sc (III) and Ti (IV)) was used in place of AcOH. If a Lewis acid is used, the lithium-nitronate must also be exchanged for a silyl-nitronate (see section 1.2.4).



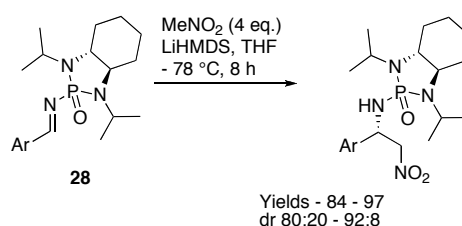
Scheme 6: Control experiments to determine the cause of enhanced selectivity

The first non-catalytic asymmetric nitro-Mannich reaction was reported in 2003 by Petrini *et al.*¹³ The reaction used a variety of non-racemic imines to control the absolute stereochemistry of the diastereoselective addition (**Scheme 7**). The imines were generated *in-situ* from α -amidoalkylphenyl sulfones **27**. High diastereoselectivity was observed in most cases, with the major product having an *anti*- relationship; however, the conditions were only demonstrated with nitromethane. In a later publication Petrini *et al.*¹⁴ expanded the scope of the nitro-species to include a wide range of cyclic and acyclic primary and secondary nitroalkanes. Again the imine was formed *in-situ* from α -amido sulfones, however the nitrogen-protecting group was changed to a formyl group rather than the carbamates used previously.



Scheme 7: The use of a non-racemic imine to control absolute stereochemistry

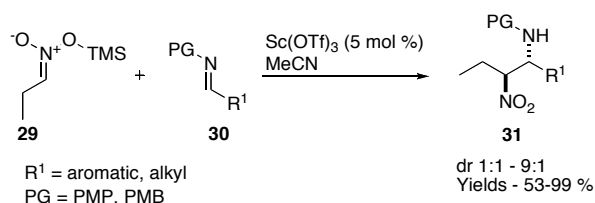
Another well-researched region in the non-catalysed area concerns the use of chiral auxiliaries incorporated into the nitrogen-protecting group. A commonly used species is the chiral sulfinyl group,¹⁵ however Li *et al.* have developed a more effective and consistent method, using chiral phosphonimine **28** (**Scheme 8**).¹⁶ The reaction was high yielding, generated consistently good dr's (~9:1) and the auxiliary could be easily cleaved using HBr.



Scheme 8: Chiral phosphonimine **28** auxiliary controlled diastereoselective nitro-Mannich reaction

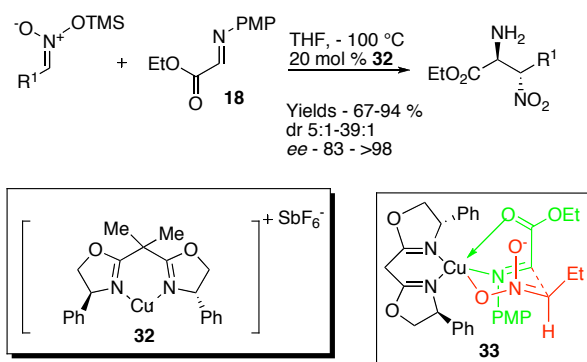
1.2.4 Indirect Metal Catalysed Reactions

A large number of groups have used an indirect metal catalysed reaction. This involves the use of a silyl-nitronate, in an analogous fashion to the Mukaiyama aldol reaction.¹⁷ The first such example was published by Anderson *et al.* in 2000 (**Scheme 9**).¹⁸



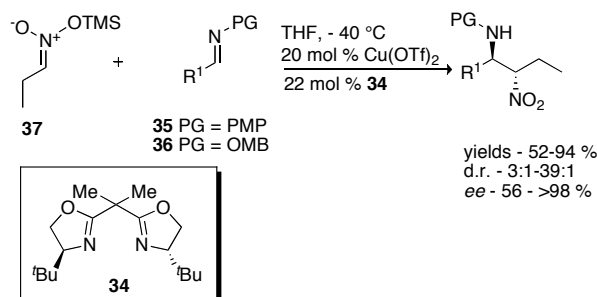
Scheme 9: The first indirect nitro-Mannich reaction

The addition of pre-formed silyl-nitronate **29** to PMP or PMB protected imines **30** provided β -nitroamines **31** in good to excellent yields. The diastereoselectivities were relatively low, but it was observed that the PMP protected imines provided a higher level of diastereoselectivity compared to the PMB protected imines. The Anderson group's silyl-nitronate methodology, and PMP protecting group, was utilised to good effect by Jørgensen *et al.*¹² The yields and selectivities achieved were exceptionally high, but the methodology is limited to a single imine **18** (Scheme 10). The protocol used 20 mol % of a copper *bis*-oxazoline catalyst **32** and achieved high *ee*'s. The authors attributed this to the ability of the imine to co-ordinate in a bidentate fashion to the copper centre, increasing the rigidity of transition state **33**; however, this limits the methodology to the single imine.



Scheme 10: The first indirect asymmetric nitro-Mannich

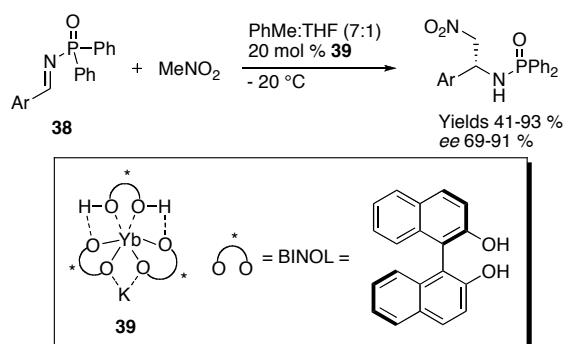
Following on from their earlier work on an indirect coupling strategy,¹¹ the Anderson group published an improved, asymmetric version.^{19 11} Having had previous success with the OMB group showing higher selectivity, the new procedure returned to the use of the PMP group, as the background non-catalysed reaction was virtually non-existent (**Scheme 11**). The system utilised similar ligands to those described by Jørgensen,¹² however, the methodology isn't limited to glyoxylate imine **18**. The system used copper (II) and a *t*Bu-BOX ligand **34**, and provided the β -nitroamines in excellent yield and stereoselectivity. The higher level of enantioselectivity of the PMP protected imines **35** over the OMB imines **36** was accredited to the differing reactivities of the imines. It was shown that TMS-nitronate **37** would react with imine **36** in the absence of the Lewis acid catalyst. The PMP protected imine **35**, however, showed very little reactivity without the Lewis acid activator. The greater reactivity of imine **36** allowed for an uncatalysed, racemic background reaction, which lowered the *ee*'s.



Scheme 11: An improved asymmetric indirect nitro-Mannich reaction

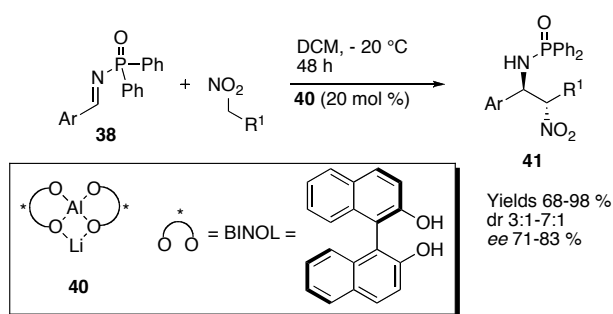
1.2.5 Direct Metal-Catalysed Reactions

The previously discussed reactions (section 1.2.4) all utilise pre-formed silyl-nitronates as the reactive partner. This does, however, necessitate an additional step and isolation procedure. This section will discuss the coupling of nitroalkanes to imines where the nitronate is generated *in-situ*, through the incorporation of a base within the reaction conditions, or the use of the nitronic acid tautomeric form of the nitroalkane. Shibasaki *et al.* published the first catalytic asymmetric nitro-Mannich reaction in 1999.²⁰ They showed that nitromethane could be coupled to *N*-Phosphinoyl imines **38** in the presence of a heterobimetallic complex **39** (Scheme 12). The catalyst contains Brønsted basic and Lewis acidic sites, as well as a chiral component, in the form of BINOL. It is believed the Brønsted basic site deprotonates nitromethane, whilst the Lewis acid site activates the imine towards reaction. Whilst the *ee*'s achieved were high, the reaction requires 20 mol % metal and 60 mol % BINOL, and suffers from very long reaction times (3-7 days) at cryogenic temperatures. The catalyst system is also limited to the use of nitromethane, and is relatively low yielding if the imine contains electron-rich or alkyl substituents.



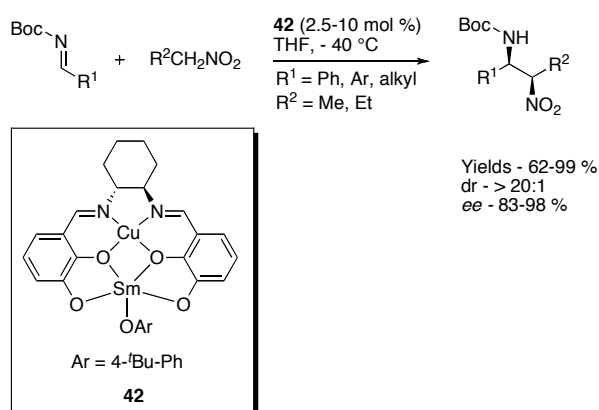
Scheme 12: The first direct catalytic enantioselective nitro-Mannich reaction

These shortcomings were addressed in 2001 when Shibasaki released an improved protocol.²¹ Firstly the nitroalkane limitation was addressed. It was suggested that the active site for the deprotonation of the nitroalkane in the original complex was too small to accommodate a larger alkyl chain. It was thought that a modified catalyst with two BINOL ligands round the metal centre rather than the three in catalyst **39** might provide a larger pocket. The group disclosed catalyst **40** as the replacement. The catalyst still contains the dual activation of a Brønsted basic and a Lewis acidic site, however the lower number of ligands allows for larger nitroalkanes to fit into the active site. The catalyst also requires shorter reaction times (48 h), and provides the *anti*-rich β -nitroamines **41** in good *ee* and diastereoselectivity.



Scheme 13: An improved heterobimetallic catalyst for the nitro-Mannich reaction

The reaction was again updated in 2007 when Shibasaki *et al.* published the first *syn*-selective nitro-Mannich reaction.²² The methodology once again uses a heterobimetallic catalyst **42**, using copper and samarium as the metal centres (**Scheme 14**). Whilst the previous systems used BINOL as the chiral ligand, to achieve the *syn*-selectivity a chiral Schiff base ligand was employed. The reaction can tolerate both electron rich and poor aromatic systems, and enolisable groups on the imine, and is effective for nitroethane and nitropropane.



Scheme 14: The first *syn*-selective nitro-Mannich reaction

Although the active species of the reaction is unknown, it is proposed to be a monomer. Mass spectrometric evidence shows in the absence of 4-*tert*-butylphenol a mixture of trimeric and oligomeric complexes are present, whilst with the additive a monomeric species is observed. If 2,6-di-*tert*-butylphenol is used significantly lower *ee*'s are seen, indicating the additive is not simply a proton source. Once again it is assumed the catalyst plays two roles, the Brønsted basic Sm-OAr deprotonating the nitroalkane whilst the Lewis acidic Cu binds to the imine. The *syn*-selectivity is proposed to arise through the sterically less congested transition state **43a** rather than **43b** (Figure 2).

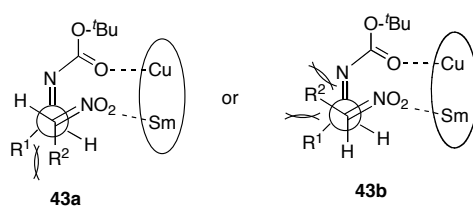
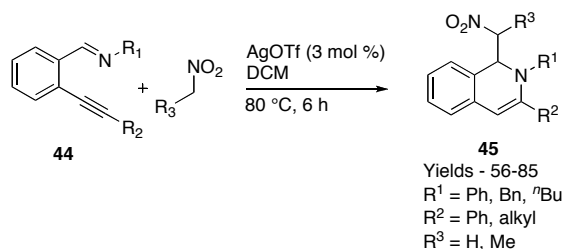


Figure 2: Proposed transition state to account for the unusual *syn*-selectivity

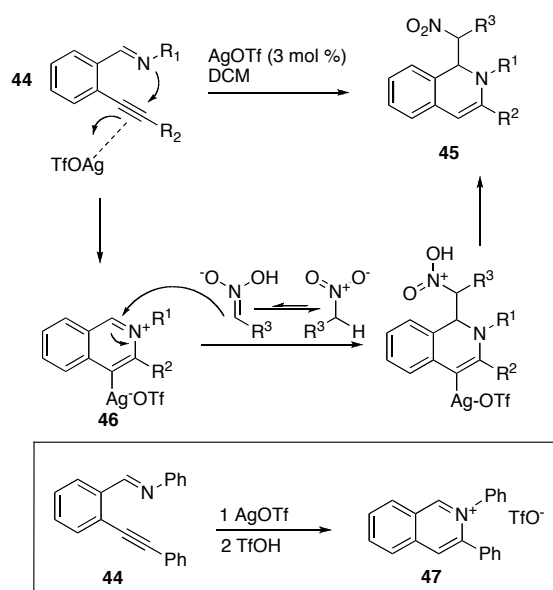
Asao *et al.*²³ described an elegant approach to the synthesis of β -nitroamines using silver triflate as a catalyst. It was shown that pronucleophiles, such as

nitromethane, would add to imines **44** to provide dihydroisoquinolines **45** in good yields (**Scheme 15**).



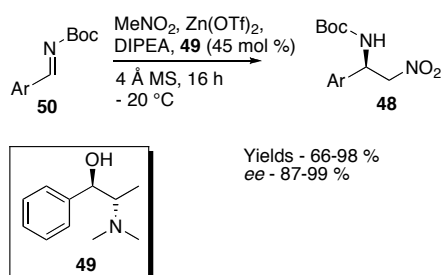
Scheme 15: Silver triflate catalysed addition of nitroalkanes to imines **44**

It was hypothesised that the silver triflate activates the imine through an intramolecular cyclisation to provide iminium **46**. Once formed, the more reactive iminium ion **46** couples with the nitro-alkane through the nitronic acid tautomer (**Scheme 16**). This theory was supported by the isolation of the isoquinolinium salt **47** when the reaction was performed in the absence of a pronucleophile, and treated with triflic acid. The reaction can tolerate alkyl and aromatic groups on the imine, as well as on the alkyne, and the pronucleophile is not limited to nitroalkanes, but includes malonates, acetone and acetonitrile.



Scheme 16: Proposed mechanism for the formation of dihydroquinoline **45**

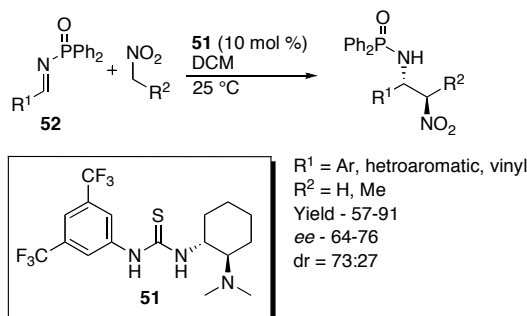
Palomo *et al.* released a simple enantioselective procedure for the preparation of *N*-Boc- β -nitroamines **48** using $\text{Zn}(\text{OTf})_2$ (30 mol %) and *N*-methylephedrine **49** as a low cost source of chirality, albeit in high loadings (45 mol %). The reaction is limited in terms of scope; only tolerating nitromethane and aryl *N*-Boc imines **50**; however, the yields and enantioselectivities are uniformly high (**Scheme 17**).



Scheme 17: A simple enantioselective nitro-Mannich reaction

1.2.6 Organocatalytic Reactions

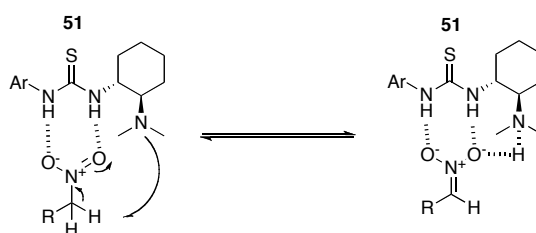
In recent years there has been a trend towards the development of organocatalytic reactions, and the nitro-Mannich reaction is no exception. The driving forces for research into this area are that organocatalysts tend to be cheaper, less toxic and more tolerable to moisture and air than metal-based systems. The first example of organocatalysis for the nitro-Mannich reaction came in 2004, when Takemoto *et al.*²⁴ showed thiourea **51** was an efficient catalyst for the coupling of nitromethane (and one example of nitroethane) to *N*-phosphinoyl imines **52** (**Scheme 18**). The *N*-phosphinoyl group was the only protecting group that allowed for high yields and modest enantioselectivity, with *N*-phenyl giving no reaction and *N*-tosyl producing the β -nitroamine in good yield, but in racemic form. The reaction only tolerates non-enolisable imines, however, the electronic nature of the imine substituent does not affect the reaction in terms of either *ee* or yield.



Scheme 18: The first organocatalytic nitro-Mannich reaction

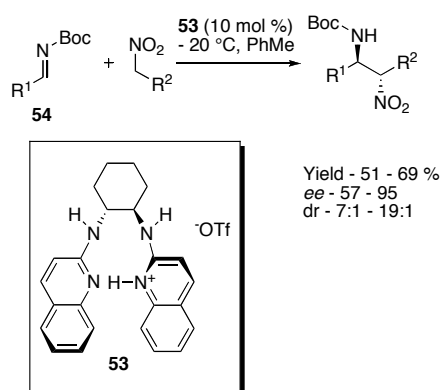
Following this publication a large number of protocols incorporating the thiourea motif have appeared, in essence making the reaction more or less effective according to the groups incorporated into the thiourea. Fundamentally the catalysts function on the same principle, as illustrated for thiourea **51** (**Scheme**

19). It is proposed that the catalyst offers dual activation. Firstly a hydrogen bonding network binds to the nitro groups oxygens, whilst the pendent tertiary amine deprotonates the acidic α -proton. Either one or both of the thiourea N-substituents provide the chiral environment. It is not the aim of this review to list the available catalysts, however, a fuller picture can be found in the recent review of Merino *et al.*²⁵



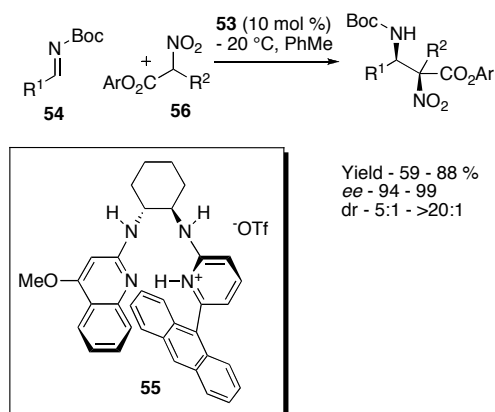
Scheme 19: Proposed mechanism for the nitro-Mannich reaction catalysed by thiourea **51**

Another area of organocatalysis utilised in the nitro-Mannich reaction is that of chiral proton catalysis. Firstly, in 2004, Johnston *et al.*²⁶ demonstrated that *bis*-quinoline **53** would effectively catalyse the coupling of non-enolisable *N*-Boc aldimines **54** with nitromethane and nitroethane (**Scheme 20**). It was found that the more electrophilic imines provided better *ee*'s ($R^1 = \text{Ph}$ *ee* = 57 %, $R^1 = m\text{-NO}_2\text{-C}_6\text{H}_4$ *ee* = 95 %), however, the diastereoselectivities remained consistently high for all substituents.



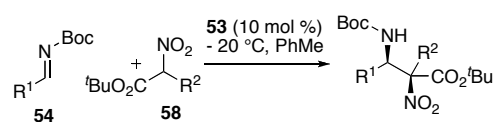
Scheme 20: A chiral proton catalysed nitro-Mannich reaction

Later, the same group disclosed an improved procedure, using a slightly modified catalyst **55** (Scheme 21). The presence of the methoxy group was found to be instrumental in the higher diastereoselectivity and ee 's observed. This increase was attributed to an enhancement in the rate of the reaction. The nature of the nitroalkane **56** was also altered to include an α -ester group. Whilst the ee 's were high with t Bu and phenyl esters, the dr's were poor (2:1). Incorporation of the 2,6-diisopropylphenyl ester group provided high levels of both diastereo- and enantioselectivity, with toluene proving to be the best solvent. The improved catalyst **55** is also capable of providing high yields, ee 's and dr's for electron rich aromatic imines (p -OMeC₆H₄, 2-furyl) **54**. Intriguingly the catalyst provides the *syn*- β -nitroamine, as proved *via* single crystal x-ray diffraction. The reason for this observed selectivity is not known, however, this work provides the first example of a *syn*-selective nitro-Mannich reaction where the β -nitro-amine contains a quaternary centre.

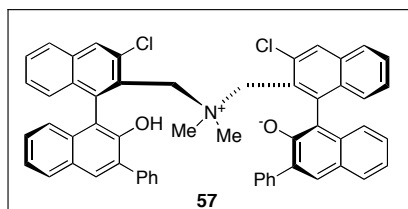


Scheme 21: An improved chiral proton catalysed nitro-Mannich reaction

In a related report Ooi *et al.*²⁷ utilise a chiral ammonium betaine **57** to catalyse a similar reaction to that shown in **Scheme 21**. A betaine, historically regarded as *N,N,N*-trimethylglycine, can be chemically defined as a neutral compound with an onium ion centre bearing no hydrogen atom and an anionic moiety that is not adjacent to the cationic site (**Scheme 22**). In this case it is postulated the proximal anion is used to deprotonate a pronucleophile, and then directs the nucleophile to a determined position through a hydrogen bonding network. The reaction achieves excellent enantioselectivities for both *syn* and *anti* products, but the diastereoselectivities are much lower than those reported by Johnston. Interestingly, pronucleophile **58** contains the *t*Bu ester, which performed poorly for Johnston. Perhaps this report is an indication that the observed *syn*-selectivity is dependent on the nature of the α -nitroester rather than the catalyst structure.

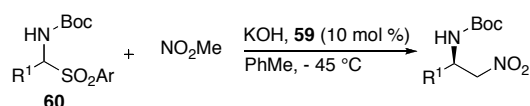


Yield - 91 - >99 %
 ee - 97 - 99 (*syn*)
 - 72 - 96 (*anti*)
 dr - 2:1 - 5:1 (*syn:anti*)

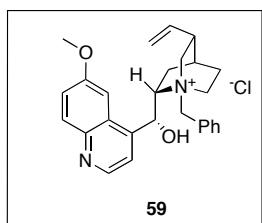


Scheme 22: A Chiral ammonium betaine-catalysed nitro-Mannich reaction

Another commonly utilised organocatalytic structure, along with the thiourea, are the Cinchona alkaloids.²⁸ The first example of this class of organocatalysis in a nitro-Mannich reaction was also the first instance of a phase transfer approach to the nitro-Mannich reaction.²⁹ Bernardi *et al.* report the use of phase transfer catalyst **59** to couple nitromethane to a variety of α -amido sulfones **60**, a well-known method of generating imines *in-situ*.³⁰ The reaction can tolerate enolisable imines, as well as a range of aromatic and heteroaromatic imines in high yields and enantioselectivities (**Scheme 23**).

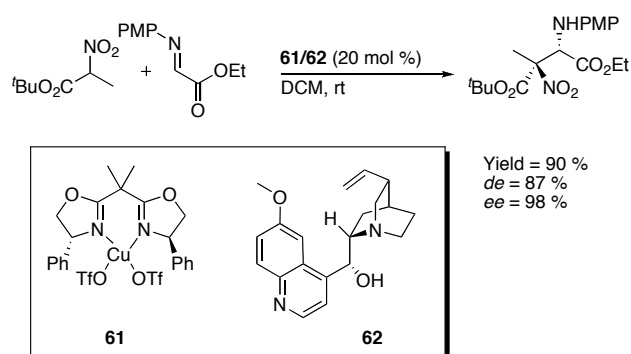


Yields - 75 - 98 %
 ee - 76 - 98 %



Scheme 23: The first phase transfer catalysed nitro-Mannich reaction

In an intriguing report by Jørgensen *et al.*³¹ organocatalysis is combined with chiral Lewis acid catalysis to afford excellent results (**Scheme 24**). Through a series of control experiments the group were able to show that the Lewis acid (a copper triflate-(*S*)-Ph-BOX based system **61**) controlled the absolute stereochemistry, whilst the cinchona catalyst **62** deprotonates the nitroalkane and controls the relative stereochemistry. If the two systems are “matched” the results are excellent.

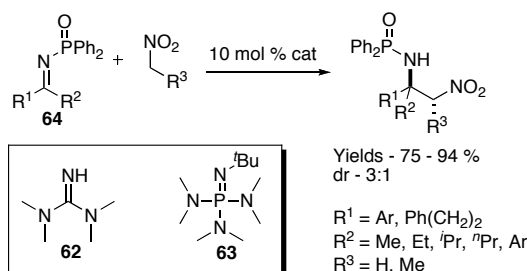


Scheme 24: A Lewis acid/organocatalytic nitro-Mannich reaction

1.2.7 Couplings Involving Ketimines

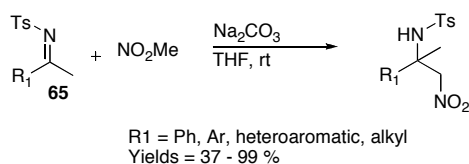
There are relatively few efficient procedures for the nitro-Mannich reaction using ketimines, the vast majority of protocols either do not test these challenging substrates, or fail to give a high yielding result.¹⁵ However, there are two procedures that are simple and efficient for this reaction. The first, reported by Terada *et al.*³² involves the use of a simple guanidine base **62** or, slightly less efficiently, a phosphazene base **63** (**Scheme 25**). The reaction tolerates a wide range of aromatic (electron rich and poor) and alkyl *N*-phosphinoyl ketimines **64**, and the yields are excellent (75 - 96 %) in all cases when coupled with nitromethane. If nitroethane is used the yields remain high, but the

diastereoselectivity is slightly disappointing (3:1). The excellent results and simple nature of the catalysts makes these conditions amiable to the possibility of rendering the reaction enantioselective with the introduction of chirality into the catalysts.



Scheme 25: A guanidine or phosphazene catalysed nitro-Mannich reaction with ketimines

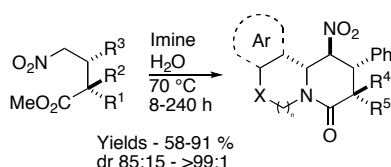
The second method, reported by Feng *et al.*³³ uses an inorganic base as the sole reagent to couple nitromethane to a selection of *N*-tosyl ketimines **65** (Scheme 26). The reaction was found to give the best results when ten equivalents of nitromethane were employed. The reaction scope encompasses a wide range of aromatic, heteroaromatic and alkyl groups, and is uniformly high yielding, with the exception of *p*OMe-C₆H₄ (37 %). In the cases where the second substituent of the ketimine was ethyl or cyclohexyl, or a higher homologue nitroalkane was employed, no reaction was observed.



Scheme 26: A nitro-mannich reaction between nitromethane and ketimines

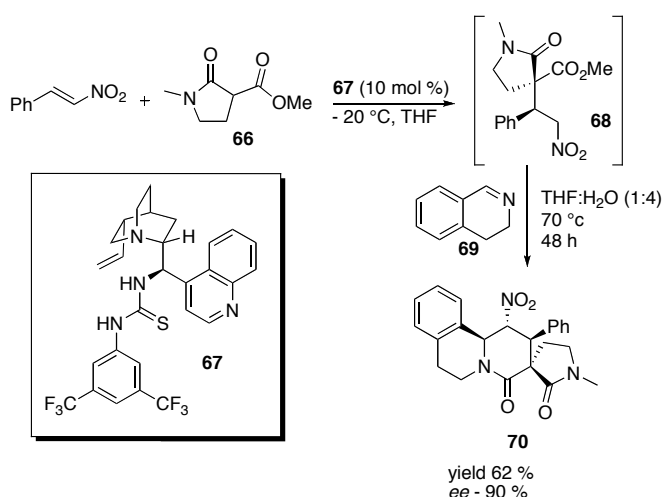
1.2.8 The Nitro-mannich Reaction Within Domino and Tandem Sequences

At the onset of this research project there were only two literature examples of the nitro-Mannich reaction being incorporated into a tandem sequence (an unexpected 1,4-addition/nitro-Mannich reaction, **Scheme 33**, and a synthesis of piperidones, **Scheme 4**). In recent years, with the view of increasing the molecular complexity of products in fewer steps, many domino and tandem reactions have been developed, and once again the nitro-Mannich reaction has seen a number of developments in this area. The first such example came in 2008, when Dixon *et al.*³⁴ disclosed a nitro-Mannich/lactamisation cascade for the synthesis of multicyclic piperidone derivatives. Excellent diastereoselectivities and yields were observed for a large number of substrates (**Scheme 27**).



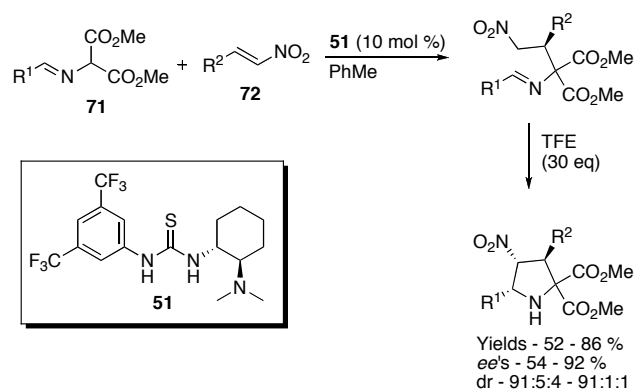
Scheme 27: A one-pot nitro-Mannich/lactamisation reaction

The reaction was taken one step further, and rendered asymmetric, by the inclusion of an asymmetric Michael addition at the beginning of the cascade (**Scheme 28**). The addition of lactam **66** to β -nitrostyrene using thiourea **67** as an asymmetric catalyst provides Michael addition product **68**. At this point bicyclic imine **69** is added to the reaction flask, along with water (water was found to be beneficial to the nitro-Mannich/lactamisation, but a hindrance to the Michael addition). The reaction was then heated at 70 °C for 48 hours to provide **70** in good yield (62 %) and excellent *ee* (90 %).



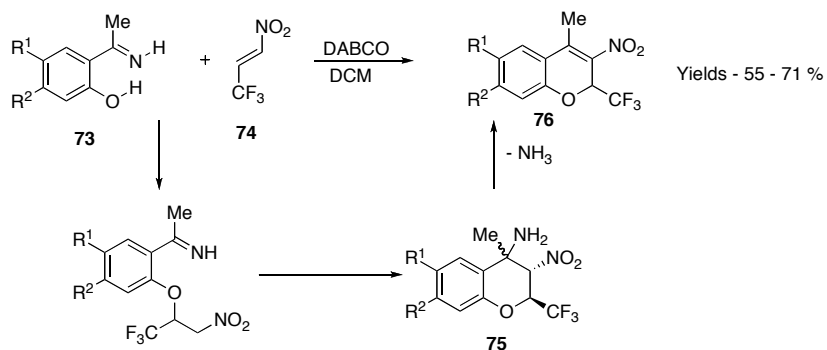
Scheme 28: A one-pot Michael addition/nitro-Mannich/lactamisation sequence

In a similar vein is the report of Takemoto *et al.*³⁵ Described as a formal [3+2] cycloaddition between azomethine ylides **71** and β -nitrostyrenes **72**, the reaction actually constitutes a Michael addition followed by a nitro-Mannich reaction (**Scheme 29**). The authors were also able to demonstrate that the thiourea catalyst **51** was instrumental in both steps of the reaction, as opposed to the methodology developed by Dixon (**Scheme 28**), where only the Michael addition is catalysed. The reaction is general in terms of the nitrostyrene portion; however, an electron rich group on the azomethine portion dramatically affects the enantioselectivity (50 % compared to greater than 80 %).



Scheme 29: A tandem Michael addition/nitro-Mannich reaction

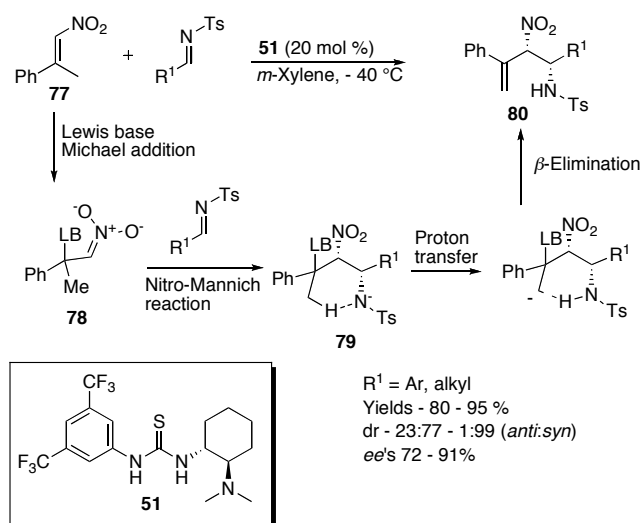
A similar approach has been adopted by Sosnovskikh *et al.*³⁶ In this case an oxa-Michael addition followed by a nitro-Mannich reaction transforms 2-hydroxyacetophenone derivatives **73** and trifluoromethyl nitroalkene **74** into intermediates **75** (**Scheme 30**). Subsequent, and spontaneous, elimination of ammonia delivers the desired chromenes **76**.



Scheme 30: The synthesis of chromenes *via* a tandem addition/nitro-Mannich/elimination mechanism

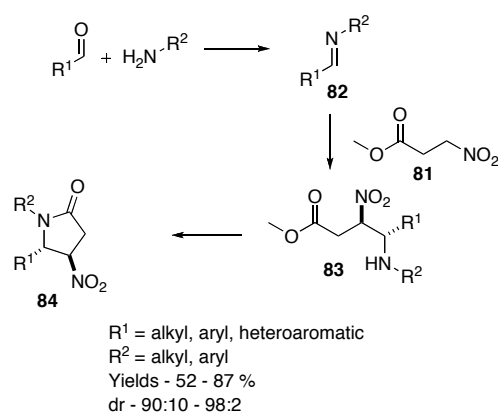
Another report detailing the use of β -nitrostyrenes within a tandem nitro-Mannich sequence was reported by Xu *et al.*³⁷ Addition of thiourea **51**, through the Lewis basic tertiary amine, to β -nitrostyrene **77** generates intermediate **78**,

which is then able to undergo a nitro-Mannich reaction with *N*-tosyl imine **79**. Finally an intramolecular proton shift followed by β -elimination furnishes β -nitro- γ -enamines **80** in excellent yields and good *ee* (**Scheme 31**). Interestingly, the nitro-amine functionality shows the unusual *syn*-stereochemistry, confirmed by single crystal X-ray diffraction, although no rational for the selectivity is presented.



Scheme 31: An Aza-Morita-Baylis-Hillman reaction of nitroalkenes and *N*-tosyl imines

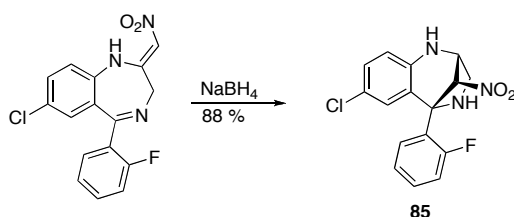
Finally, in an extension to their previous work on nitro-Mannich/lactamisation cascades (**Scheme 28**), and similar in nature to Jain's work (**Scheme 4**), Dixon *et al.*¹⁰ reported the synthesis of pyrrolidinones *via* a similar reaction pathway as used previously for the synthesis of piperidinones (**Scheme 28**). In this report methyl-3-nitropropanate **81** undergoes a nitro-Mannich reaction with imines **82**, formed *in-situ* from condensation of aldehydes and amines. Cyclisation of the resultant amine **83** onto the methyl ester provides pyrrolidinones **84** in good yield and excellent diastereoselectivity (**Scheme 32**).



Scheme 32: The synthesis of pyrrolidinones *via* a nitro-Mannich/lactamisation cascade

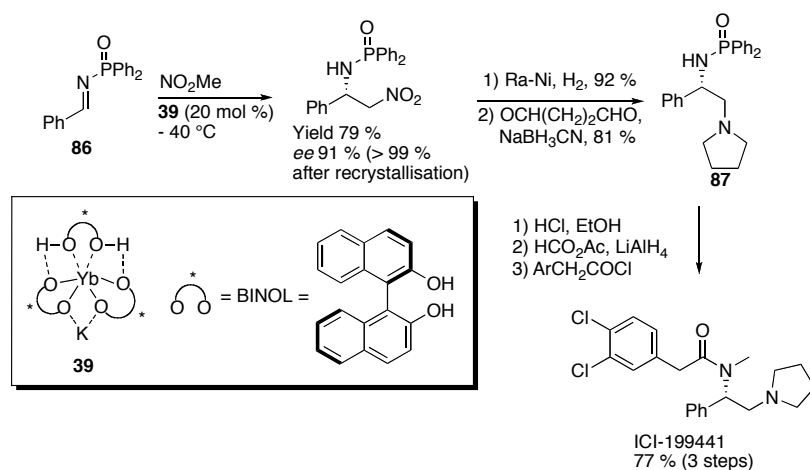
1.2.9 Synthetic Applications of the Nitro-Mannich reaction

To date, the nitro-Mannich reaction has had little popularity within target synthesis. Perhaps this is due to the fact that only recently have effective diastereo- and enantio-selective protocols been released. The first report of a nitro-Mannich reaction in synthesis dates back to 1978, when Walser *et al.*³⁸ reported an unexpected nitro-Mannich reaction whilst investigating the synthesis of imidazobenzodiaepines. Although the cyclisation was unexpected, it provided β -nitroamine **85** in good yield and as a single diastereoisomer (**Scheme 33**).



Scheme 33: An unexpected nitro-Mannich cyclisation

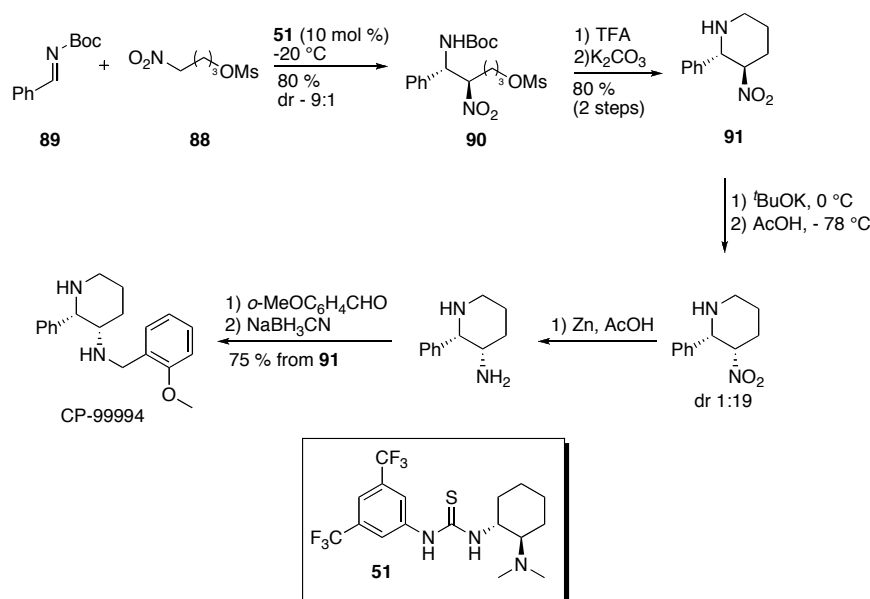
The first deliberately employed nitro-Mannich reaction was published in 2002, when Shibasaki *et al.*³⁹ reported the synthesis of ICI-199441, a potent κ -opioid agonist.⁴⁰ The synthesis begins with the nitro-Mannich reaction of nitromethane and *N*-phosphinoyl imine **86**, catalysed by heterobimetallic complex **39**. Hydrogenation over Raney nickel followed by reductive alkylation formed pyrrolidine **87**. Finally acidic deprotection of the phosphinoyl group, reductive methylation and acylation provided ICI-199441 in just six steps and 35 % overall yield (Scheme 34).



Scheme 34: The nitro-Mannich based approach to ICI-199441

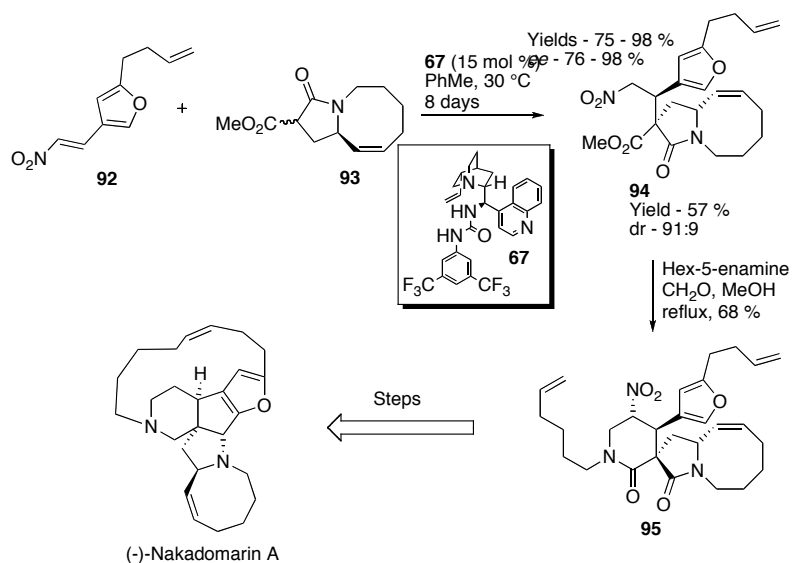
In the same publication is detailed the synthesis of CP-99994, a potential anti-emetic, *via* a nitro-mannich route; however, a more concise route, again utilising a nitro-Mannich disconnection, is described by Takemoto *et al.*⁴¹ The synthesis begins with an organocatalysed nitro-Mannich reaction between nitroalkane **88** and *N*-Boc imine **89**. The product β -nitroamine **90** was isolated as a 9:1 mixture of diastereoisomers (*anti:syn*) in 80 % yield. The mixture was subjected to acidic deprotection followed by cyclisation to afford piperidine **91** in the same diastereomeric ratio. Epimerisation by kinetic protonation increased the ratio to

1:19 (*anti:syn*) in favour of the desired isomer. The mixture was subjected to reduction of the nitro group immediately to avoid isomerisation and the final alkyl group introduced *via* reductive alkylation to provide CP-99994 in five steps and 48 % yield (**Scheme 35**).



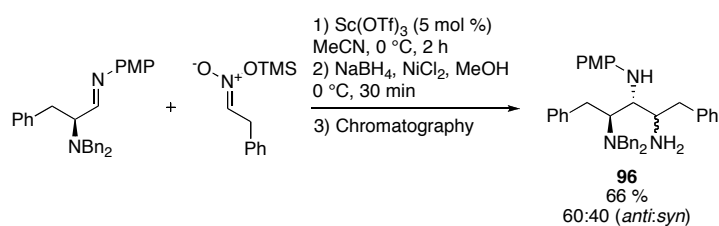
Scheme 35: Takemoto's total synthesis of CP-99994

More recently Dixon *et al.* utilised their previously developed nitro-Mannich/lactamisation methodology³⁴ within the synthesis of (-)-Nakadomarin A (**Scheme 36**).⁴² Coupling of nitro-alkene **92** to pro-nucleophile **93** under the group's organocatalytic conditions provided nitro-Mannich precursor **94**. The nitro-Mannich reaction between **94** and an *in-situ* generated imine, followed by subsequent lactamisation provides spirocycle **95** in good yield (68 %). Subsequent removal of the nitro group, selective lactam reduction and furan/iminium cyclisation and a final Grubbs ring closing metathesis furnished (-)-Nakadomarin A, in 16 steps overall (longest linear sequence 12 steps).



Scheme 36: The key nitro-Mannich/lactamisation step in the synthesis of (-)-Nakadomarin A

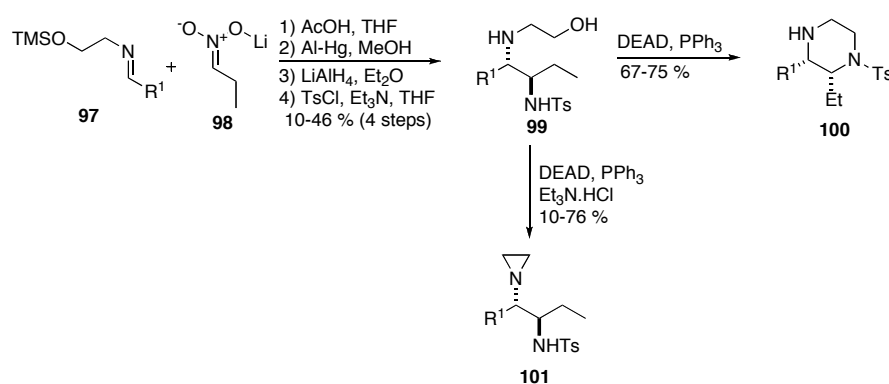
Bernardi *et al.*⁴³ have reported the use of the nitro-Mannich reaction to synthesise *pseudo*-C₂-symmetric triamines **96** for use in HIV protease inhibition (**Scheme 37**). This work also provides the first instance of a nitro-Mannich reaction with an imine containing an α -stereocentre. Unfortunately the reaction shows little diastereoselectivity (60:40). Subsequent nickel boride reduction provides triamine **96** in 66 % yield as a chromatographically separable mixture of epimers.



Scheme 37: The preparation of *pseudo*-C₂-symmetric triamines *via* a nitro-Mannich reaction

Anderson *et al.*⁴⁴ explored the synthesis of piperazines using nitro-Mannich products (**Scheme 38**). Acetic acid promoted nitro-Mannich coupling of imine

97 to lithium nitronate **98** furnishes the β -nitroamine in excellent yield and diastereoselectivity (87 %, dr >19:1). Subsequent two-step reduction followed by protection of the primary amine as the tosylate provides vicinal diamine **99**. Ensuing Mitsunobu cyclisation furnished piperazine **100** in good yield. It was also found that the addition of Et₃N.HCl changed the mode of cyclisation to provide aziridine **101**. This change in cyclisation is attributed to whether the *N*-tosyl amine is deprotonated (in the absence of Et₃N.HCl) or not, and thus which amine is more nucleophilic.



Scheme 38: Cyclisation of nitro-Mannich products to furnish piperazines or aziridines

1.3 Conjugate Additions to Nitro-Alkenes

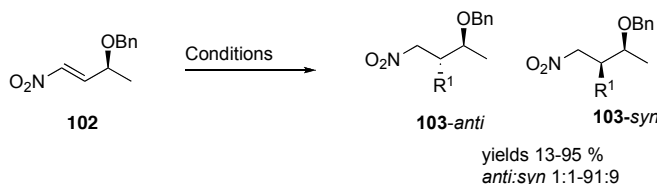
1.3.1 Overview

The addition of nucleophiles to Michael acceptors is an important reaction for the synthesis of highly functionalised synthetic building blocks. Nitro-alkenes stand out amongst Michael acceptors due to the synthetic versatility of the nitro group. Often described as a “synthetic chameleon”,⁴⁵ the nitro group can be transformed into a large number of different functional groups. The Nef reaction,⁴⁶ reduction to an amine,⁴⁷ and nucleophilic displacement⁴⁸ are only a few examples of possible transformations. The range of nucleophiles employed in Michael additions to nitro-alkenes is extensive, and includes carbon, oxygen, nitrogen, phosphorus and sulphur based examples.⁴⁹ Of most importance, however, are those that impart chirality to the new molecule. These reactions can be divided into those that utilise substrate-controlled diastereoselectivity, those that use an auxiliary-controlled approach, and those that utilise chiral catalysts. As the conjugate addition of nucleophiles to nitro-alkenes is of key importance to the research carried out, a review of the literature concerning this topic will be presented, however, it will be limited to carbon based nucleophiles. It should be noted that the addition of nucleophiles to nitro-alkenes is only one facet of their reactivity. In addition they readily react with radicals and act as dienophiles in Diels-Alder type reactions, however, these lie outside the scope of this review.⁵⁰

1.3.2 Substrate Controlled Diastereoselective Michael Additions

There are numerous examples of substrate-controlled conjugate additions of carbon nucleophiles to nitro-alkenes. In this case a chiral centre already present in the nitro-alkene influences the stereochemical outcome of the reaction. A selection of the more sophisticated examples will be discussed in the following pages. A more detailed picture can be gained from the review of Barrett.⁵¹

Cossío *et al.* reported the addition of organometallic nucleophiles to optically active nitro-alkene **102** in a stereoselective fashion, to yield the *anti*-diastereoisomer **103**.⁵² The authors noticed that whilst Grignard and organolithium reagents (phenyl and methyl) showed some diastereoselectivity, the best results were obtained using lithium organocuprates of the type LiR_2Cu (**Scheme 39**).



Scheme 39: The addition of organometallic reagents to chiral nitro-alkenes

The observed stereochemical outcome is explained using a model proposed by Dorigo *et al.*⁵³ whereby an electron-donating group in the *anti*-position (with respect to the incoming nucleophile) in the transition state is favoured (**Figure 3**). The lowest energy transition states were calculated, using a hydroxyl group as an approximation for the *O*-benzyl group, as having the proton in the *anti*-position, the methyl inside and the hydroxyl outside (based on heat of formation

calculations), or having the methyl *anti*-, the hydroxyl inside and the proton outside (based on ΔG° calculations). The calculations, therefore, suggest that the preference for the *anti*- isomer is not related to allylic strain or Felkin-Anh geometries, but to transition states stabilised by electron donating groups *anti* with respect to the carbon-carbon bond being formed.

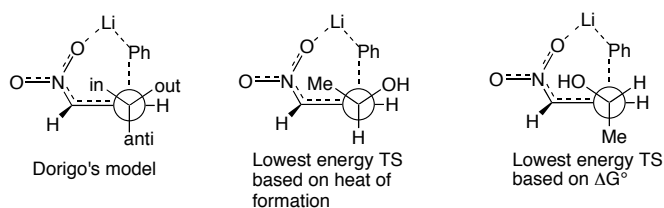
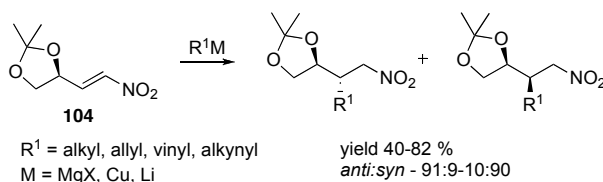


Figure 3: Model proposed to account for high levels of stereoselectivity

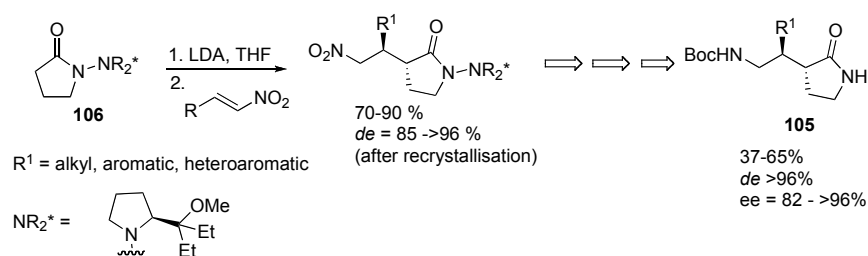
Pätzelt *et al.* reported the synthesis and subsequent 1,4-addition of a variety of organometallic nucleophiles to optically active nitro-alkene **104** (Scheme 40).⁵⁴ The nitro-alkene **104** was synthesised by a known procedure (Henry reaction followed by dehydration of the resulting nitro alcohol) from optically active glyceraldehyde. Treatment with organometallic reagents produced predominantly the *anti*-products, as observed by Cossío, however, the use of vinylmagnesium bromide resulted in a 1:9 preference for the *syn*-isomer, explained by co-ordination to the γ - oxygen. The softer nucleophilic character of the cuprates and alkynyl lithium reagents results in poor chelation, thus the *anti*-isomer is preferred.



Scheme 40: Addition of organometallic reagents to chiral nitro-alkene **104**

1.3.3 Auxiliary Controlled Michael Additions

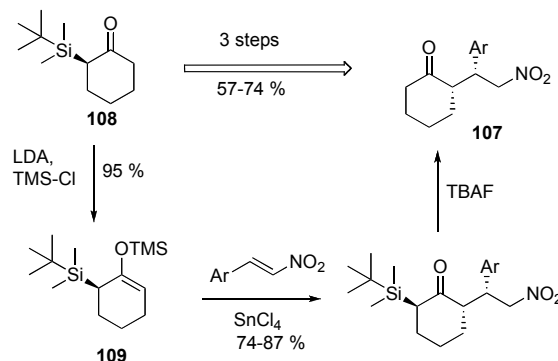
The area of auxiliary controlled Michael additions to nitro-alkenes is also a well-researched field. These reactions employ a stoichiometric amount of a chiral auxiliary, which must later be cleaved to give the desired, chiral products. Enders *et al.* described the preparation of α -(β -aminoalkyl)-substituted γ -lactams **105**, the key step being the addition of γ -lactam **106** to a nitro-alkene (**Scheme 41**).⁵⁵ A sterically demanding (*S*)-proline derived auxiliary on the lactam nitrogen provided the asymmetry. Aliphatic nitro-alkenes provided higher diastereoselectivity than the aromatic counterparts; however, recrystallisation significantly increased the *de*. Reduction of the nitro group followed by Boc protection and cleavage of the N-N bond provided lactams **105** in acceptable yields and high *de* and *ee*.



Scheme 41: Addition of γ -lactams to nitro-alkenes

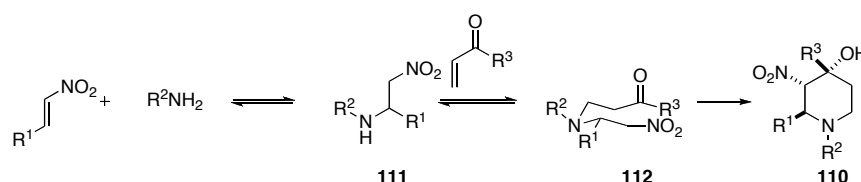
The same group synthesised a range of α,β -disubstituted γ -nitro ketones **107** by the use of enantiopure α -silylketone **108** (**Scheme 42**).⁵⁶ Conversion to the kinetic TMS enol ether **109** with LDA and TMS-Cl was achieved with no racemisation. A tin tetrachloride promoted 1,4-addition to aromatic nitro-alkenes occurred with high yields and diastereoselectivities. Cleavage of the silyl group was achieved using TBAF with a $\text{NH}_4\text{F}/\text{HF}$ buffer to yield the desired nitro-ketones **107**. The presence of the buffer was necessary to reduce epimerisation,

although a small amount was still observed. A similar protocol was employed on acyclic ketones with comparable results.



Scheme 42: Addition of α -silyl enol ether

Shi *et al.* reported the synthesis of substituted piperidines **110** through the one-pot condensation of nitro-alkenes, amines and enones (**Scheme 43**).⁵⁷ Initial 1,4-addition of the amine to the nitro-alkene generates **111**, a second 1,4-addition, this time to the enone generates **112**, which undergoes a Henry cyclisation to provide the desired piperidines **110**.



Scheme 43: Proposed one-pot cascade piperidine synthesis

It was shown that if an amine with an α -stereocentre was used, the stereocentre of the amine dictated the absolute configuration of the piperidine through exocyclic chirality induction (**Figure 4**). It is suggested that minimisation of *syn*-pentane interactions, along with p - σ^* interactions of the nitrogen lone pair

with the exocyclic axial group accounted for the observed stereocontrol. Due to the nature of the $p\text{-}\sigma^*$ interactions, it was thought that the use of a less bulky group able to provide a stronger $p\text{-}\sigma^*$ interaction would enhance the chirality induction and, as was shown with the amino esters, this was the case.

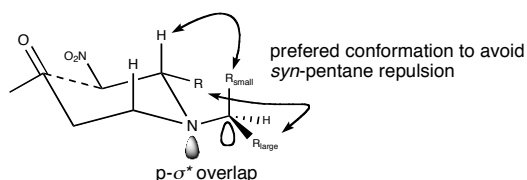
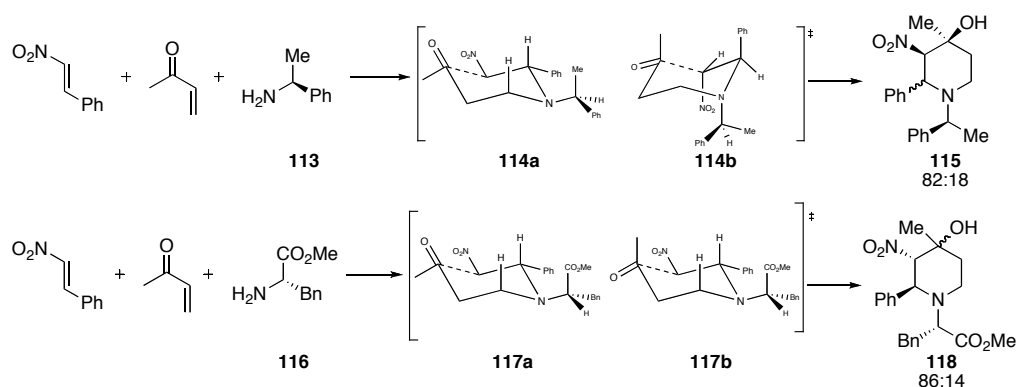


Figure 4: Proposed exocyclic chirality induction

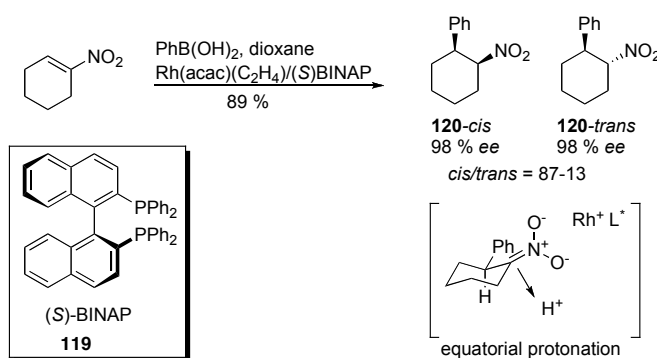
In **Scheme 44** two examples illustrating the dramatic effect changing the nature of the amine substituents had are shown. When the amine used had a methyl, phenyl and a proton, **113**, the observed dr was 82:18 (**115**), with no formation of the remaining two diastereoisomers (epimers at the hydroxyl centre). This was accounted for due to a mixture of the preferred transition state **114a**, which minimises *syn*-pentane interactions, and transition state **114b**, which has a larger *syn*-pentane interaction, but has greater $p\text{-}\sigma^*$ stabilisation of the chair transition state. If the amine used had a benzyl, proton and an ester group, **116**, the observed dr was 86:14 (**118**), again with no formation of the remaining two diastereoisomers, however, this time the only observed diastereoisomers were epimers at the hydroxyl centre. This was attributed to the chair transition states **117a** and **117b** having a much larger $p\text{-}\sigma^*$ stabilisation due to placing the ester group antiparallel to the amine lone pair, combined with the small steric bulk of this group minimising *syn*-pentane interactions.



Scheme 44: Examples of different levels of chirality induction due to the electronic nature of the amine substituents

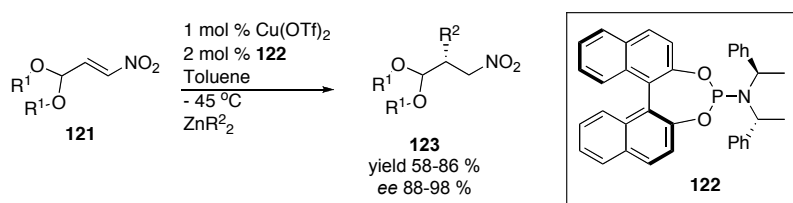
1.3.4 Enantiopure Catalyst Controlled Michael Additions

The final area of asymmetric Michael additions concerns the use of chiral catalysts. This is often the most attractive of the options for absolute stereocontrol, as the source of chirality can be used “catalytically”, unlike the previous examples where a stoichiometric amount of the auxiliary was required. Hayashi *et al.* reported that 1-nitrocyclohexene undergoes conjugate addition of phenylboronic acid in the presence of a rhodium catalyst.⁵⁸ The use of just 3 mol % of (*S*)-BINAP **119** resulted in an *ee* of 98 %. The diastereoselectivity was in favour of the thermodynamically less stable **120-cis** isomer (**120-cis**:**120-trans** 87:13), presumably arising from equatorial protonation of the rhodium nitronate (**Scheme 45**).⁵⁹ The authors also noted that treatment of the *cis* isomer with sodium bicarbonate in refluxing ethanol isomerises the product to the *trans* isomer with no loss of enantio-purity, thus allowing the synthesis of both the thermodynamically less stable *cis*-compounds, as well as the *trans* in high *ee*.



Scheme 45: Rhodium catalysed Michael addition of phenylboronic acid to 1-nitrocyclohexene

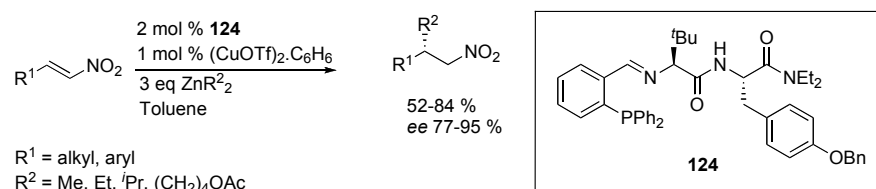
One of the most investigated conjugate additions to nitro-alkenes is the addition of dialkylzinc reagents. The first such procedure to achieve high *ee* on acyclic substrates was reported by Feringa *et al.* (**Scheme 46**).⁶⁰ The copper catalysed addition of organozinc reagents to acetal protected nitropropenes **121** in the presence of a chiral phosphoramidite ligand **122** provided the required substituted nitro-alkanes **123** in high yield and *ee*. The products were then efficiently transformed to the corresponding amino acids, aldehydes and alcohols through simple functional group interconversions.



Scheme 46: Addition of organozinc reagents to acetal protected nitro-propenes

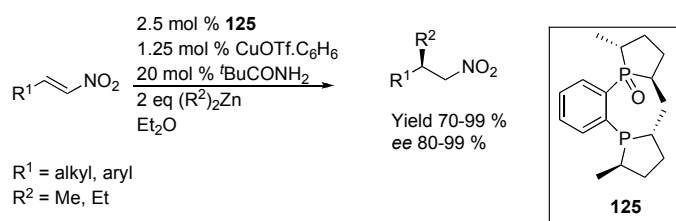
Hoveyda *et al.* reported the addition of a range of dialkylzinc reagents to nitro-alkenes in the presence of copper triflate/benzene complex and dipeptide phosphine ligand **124** (**Scheme 47**).⁶¹ Through a process of ligand screening it was shown that a diethyl amide terminus was essential for high

enantioselectivity. It was also shown that dipeptides were far superior to the mono-peptide examples. The additions proceeded at ambient temperatures and with high *ee* (77-95 %) for electron rich and poor nitro-styrenes, as well as alkyl substituted examples.



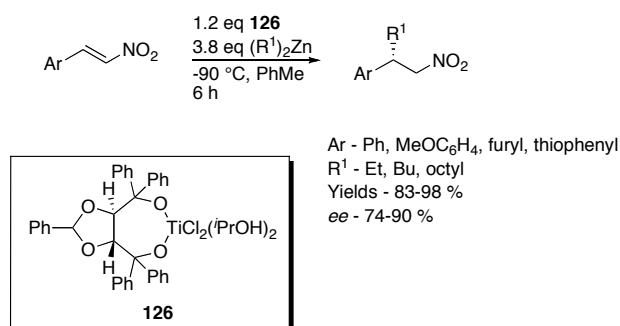
Scheme 47: Copper catalysed addition of dialkylzinc reagents to nitro-alkenes

Charette *et al.* reported the addition of dialkylzinc reagents to nitro-alkenes, using a chiral mono-oxide *bis*-phosphine ligand **125** (Scheme 48).⁶² Lower enantioselectivity were observed with the bulkier Et and i Propyl ligands, and the use of a “dummy” ligand (t BuCONH₂) to promote monomeric copper species enabled lower chiral ligand loadings. Low enantioselectivities were observed if the *bis*-oxide or Me-DuPHOS were used, indicating the importance of having high purity mono-oxide. It was also shown that pre-complexation of the ligand to copper is possible, and the air-stable solid provides similar results as the non pre-complexed reactions, but does not require the use of a glove box.



Scheme 48: Mono-oxide *bis*-phosphine-copper complex promoted addition of dialkylzinc reagents

There are many other ligand systems that catalyse the asymmetric addition of dialkylzinc reagents to nitro-alkenes, mostly using copper catalysis,⁶³ however, the addition can also be carried out in the presence of titanium. Seebach *et al.*⁶⁴ reported the use of titanium-TADDOLate complex **126** as a chiral Lewis acid for the addition of dialkylzinc reagents to a range of nitro-alkenes (**Scheme 49**). Whilst a super-stoichiometric amount of complex **126** (1.2 eq) is required for high *ee*'s, a catalytic amount (20 mol %) can be used, however, the *ee* is reduced to only 20 %.

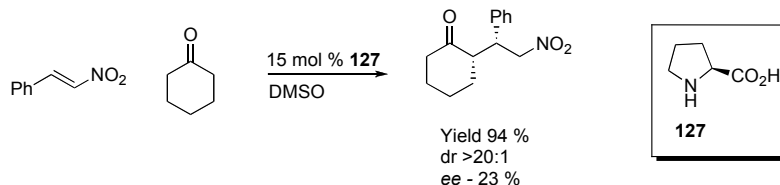


Scheme 49: Titanium-TADDOLate complex **126** induced addition of dialkylzinc reagents to nitro-alkenes

1.3.5 Organocatalysed Michael Additions

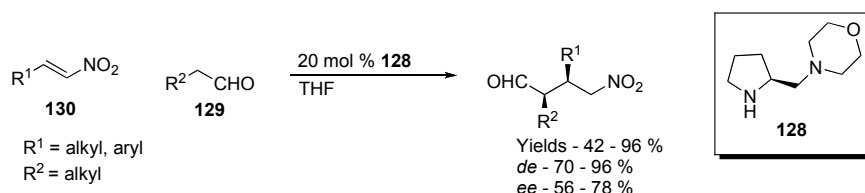
Another popular area of asymmetric catalysis, both in general and in 1,4-additions to nitro-alkenes, is that of organocatalysis.⁶⁵ One of the more popular small organic molecules used in organocatalysis, proline based catalysts are abundant in this field. Indeed the first asymmetric example of organocatalysis involving nitro-alkenes used (*S*)-proline **127** itself. List *et al.* reported the addition of cyclohexanone to nitrostyrene with 15 mol % proline.⁶⁶ Although the

addition proceeded with high yield and diastereoselectivity (>20:1), only modest enantioselectivity was observed (23 % *ee*) (**Scheme 50**).



Scheme 50: The first organocatalytic 1,4-addition to nitro-alkenes

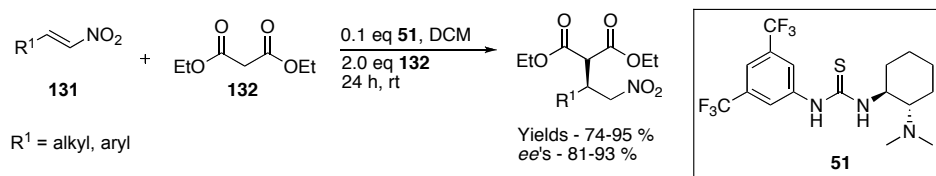
Barbas III *et al.* performed a screen on (*S*)-proline based catalysts, and discovered the morpholine derivative **128** was the most effective for the addition of aldehydes **129** to aromatic and alkyl nitro-alkenes **130**.⁶⁷ The major product was the *syn*-diastereoisomer, and was isolated in good yields with good diastereo- and enantioselectivity (**Scheme 51**).



Scheme 51: (*S*)-proline derived organocatalyst for the addition of aldehydes to nitro-alkenes

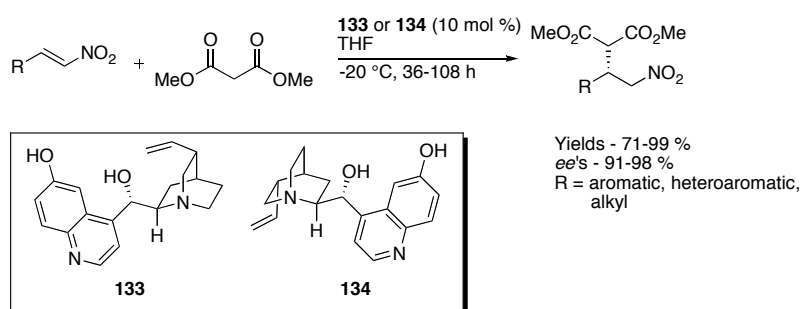
Earlier, in the section pertaining to the nitro-Mannich literature, it was shown that thiourea catalysts are able to catalyse the nitro-Mannich reaction through activation of the nitro group (**Scheme 19**). It is, perhaps, unsurprising then that the same catalysts are able to catalyse the Michael addition of malonates to nitroalkenes, again through activation of both the nitro group and by deprotonation of the acidic malonate proton. Takemoto *et al.*⁶⁸ were able to show that thiourea **51** can efficiently catalyse the addition of malonate **132** to a

range of alkyl and aromatic nitro-alkenes **131** in high yield and *ee* (**Scheme 52**). Through various control reactions the authors demonstrated that for high yields and *ee*'s the thiourea and a tertiary amine motif were both required in the same molecule.



Scheme 52: Thiourea catalysed addition of malonates to nitro-alkenes

The principle of double activation, *i.e.* activation of the electrophile and the nucleophile, from the same catalyst is not just limited to the thiourea/tertiary amine motif contained in catalysts such as **51**, but is also a postulated mode of action for another class of organocatalysts, the Cinchona alkaloids.⁶⁹ Deng *et al.*⁷⁰ reported the use of Cinchona alkaloid derivatives **133** and **134** to catalyse the addition of dimethyl malonate to nitro-alkenes in excellent yield and *ee* (**Scheme 53**). The authors demonstrated that the phenolic OH function was required for the high enantioselectivity. The reaction was not catalysed by phenol, and the authors propose that the phenolic OH activates the electrophile whilst the quinuclidine amine activates the nucleophile.

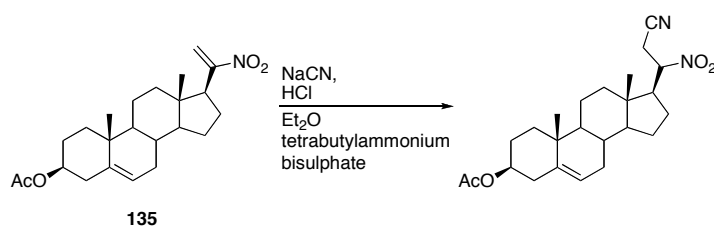


Scheme 53: Cinchona alkaloid derived organocatalytic addition of dimethyl malonate to nitro-alkenes

1.3.6 Addition of Cyanide and Related Nucleophiles

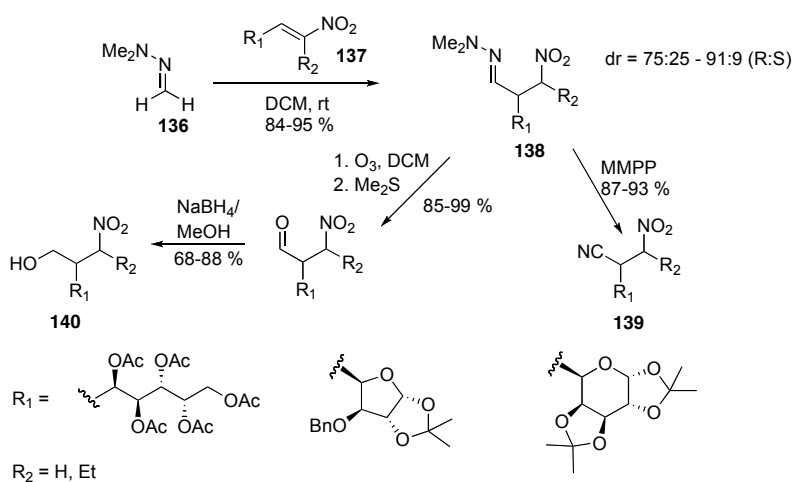
As the addition of cyanide to nitro-alkenes is of direct relevance to the research described in the Results and Discussion section, this particular nucleophile will be discussed in some detail. At the onset of this research program there was only a single example of the direct addition of a cyanide nucleophile to a nitro-alkene (**Scheme 54**),⁷¹ and one example of an indirect addition (**Scheme 55**).⁷² Since this research program has started, however, several new methodologies have been published in this area, and these will be described in the following section.

Barton *et al.* demonstrated that *in-situ* generated HCN (formed from NaCN and HCl in solution) would add to a steroidal based nitro-alkene **135** in excellent yield (97 %).⁷¹ This single example represents the first addition of a cyanide anion to a nitro-alkene in the literature.



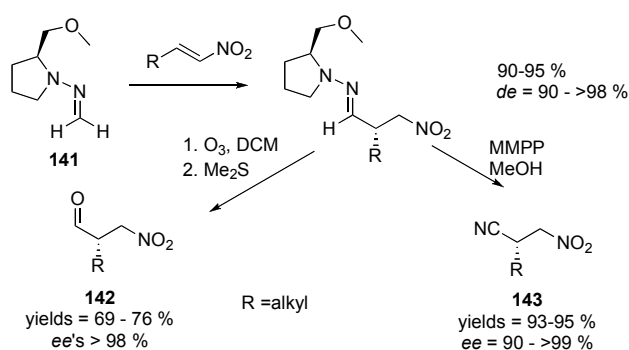
Scheme 54: The first reported 1,4-addition of a cyanide anion to a nitro-alkene

During the development of a new formyl anion equivalent, Lassaletta *et al.* looked at the addition of formaldehyde dimethylhydrazone **136** to carbohydrate-derived nitro-alkenes **137** (**Scheme 55**).⁷² The reaction proceeded under mild conditions, and gave the desired 1,4-addition products **138** in excellent yield and with high diastereofacial selectivity. This selectivity stems from the carbohydrate component, and both diastereoisomers could be separated by chromatography. Further reactions converted the hydrazones to the corresponding β -nitronitriles **139** or 1,3-nitro alcohols **140**, with no racemisation observed.



Scheme 55: Substrate controlled 1,4 addition of formaldehyde dimethylhydrazone

In an extension of the work previously carried out by Lassaletta *et al.* (**Scheme 55**), simply changing the nitrogen substituents of the hydrazine from dimethyl to a chiral entity **141**, in this case based on (*R*) or (*S*) proline, directly induced asymmetry into the 1,4-addition.⁷³ Again ozonolysis or oxidative cleavage of the auxiliary provided the nitro-aldehyde **142** and β -nitronitriles **143** in good yields and high *ee*'s (**Scheme 56**).



Scheme 56: Formaldehyde SAMP-hydrazine auxiliary controlled additions to nitro-alkenes

A mechanism was proposed to explain the high diastereoselectivity during the 1,4-addition and the observed absolute stereochemistry of the products. The authors proposed the reagent attacks the *Si* face of the nitro-alkene, and forms a closed, chair-like transition state. This transition state is stabilised by the electrostatic interactions between the developing charges of $N^{\delta+}/NO_2^{\delta-}$ (**Figure 5**).

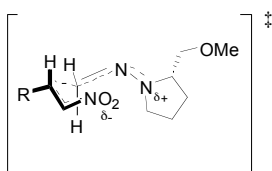
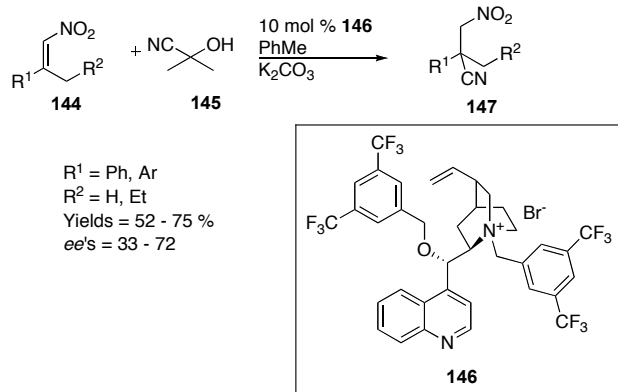


Figure 5: Proposed transition state

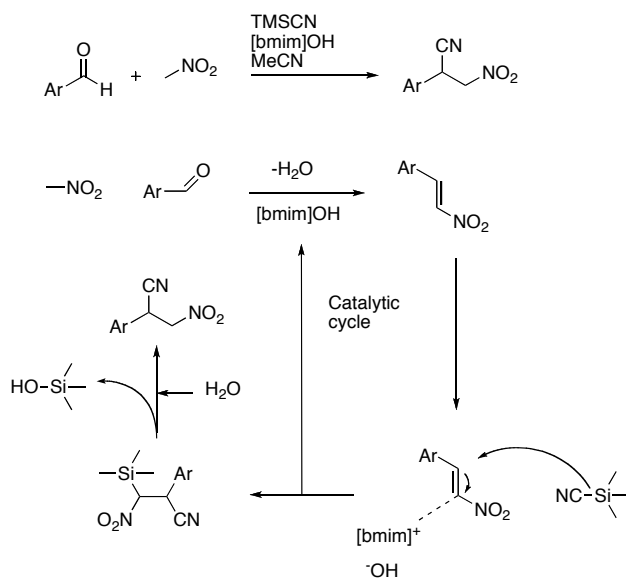
In a further experiment, double induction with both chiral Michael acceptors (carbohydrate based nitro-alkenes as shown in **Scheme 55**) and donors (formaldehyde SAMP/RAMP-hydrazone) were used. They discovered that in the case of the “matched” pairing excellent (>96 % *de*) diastereoselectivity resulted, however, with the “mismatched” pair much lower (38-68 % *de*) selectivity was observed. In this case the configuration of the new centre was opposite to that induced by the carbohydrate moiety, indicating a strong dominance of induction by the SAMP/RAMP auxiliary over the carbohydrate.

Ricci *et al.* reported the organocatalysed addition of cyanide to nitro-alkenes **144** using acetone cyanohydrin **145** under phase transfer conditions (**Scheme 57**).⁷⁴ Initially, using catalysts described by Soós,⁷⁵ little to no activity was observed. This was attributed to the lack of cyanide generation under the homogeneous condition. Under the phase transfer conditions (inorganic base/organic solvent), and in the presence of quaternary ammonium salt **146** the reaction was effected to provide nitro-alkanes **147** containing an all-carbon quaternary centre with modest yields (52-75 %) and *ee* (33-72 %). A selection of cyanohydrins was explored, and it was shown that an increase in size (benzophenone and fluorenone cyanohydrin) led to an erosion of enantioselectivity. The authors believe this may be due to the catalyst accommodating an anionic species more complex than a CN ion.



Scheme 57: Phase transfer addition of cyanide to nitro-alkenes

Yadav *et al.* reported the addition of cyanide to *in-situ* formed nitro-alkenes promoted by the use of an ionic liquid (**Scheme 58**).⁷⁶ The reaction consists of a three component coupling, combining nitro methane, an aromatic aldehyde and cyanide (in the form of TMS-CN) in the presence of an ionic liquid ([bmim]OH). The authors suggest the mechanism outlined in **Scheme 58**.



Scheme 58: Ionic liquid promoted three-component coupling of aldehydes, nitromethane and cyanide

1.4 Electrophilic Additions Involving an α -Stereocentre

The last topic to be covered in this review of relevant literature is the diastereoselectivity of electrophilic attack on a trigonal carbon adjacent to a stereogenic centre. Many studies have been made on cyclic enolic systems, where the selection of the path of least hindered approach is relatively straightforward, and results can be predicted with some accuracy.⁷⁷ In contrast, it is much harder to predict the outcome for an acyclic system. The difficulty lies in the fact that in these systems there is greater conformational freedom about the central carbon-carbon single bond, due to free rotation around this bond (**Figure 6**).

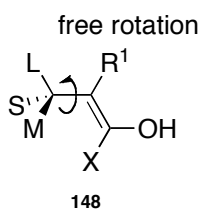


Figure 6: Example of an acyclic enol with free rotation

The most reactive conformation of the system towards electrophilic attack will determine the favoured stereochemical outcome of the resultant product. Thus, if one can predict the most reactive conformation, it will be possible to predict the relative stereochemistry of the products. There are several seminal papers discussing this topic, and they will each be discussed in turn. The first proposed solution to this problem was presented by Zimmerman *et al.* in 1959,⁷⁸ when they initially looked at the preferred conformation of acyclic enols such as **148** ($X = R$ group). This was achieved by describing the system as a tetrahedral-trigonal system **149**, and expressing the potential energy of the system as a function of the conformational angle θ (**Figure 7**). The value of θ at which the

potential energy of the system is minimised is proposed to be the reactive conformation of the system, using the assumption that an exothermic reaction (such as ketonisation) would have a transition state structure closely resembling the geometry of the starting material.

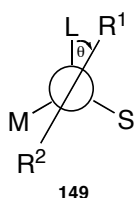


Figure 7: Depiction of Zimmerman's tetrahedral-trigonal system and conformational angle θ

In this case L, M and S represent a large, medium and small group on the tetrahedral stereocentre, R^1 represents a group on the enolic trigonal centre and R^2 represents the entire grouping $=CXOH$ shown in **Figure 6**. Using a series of calculations the researchers were able to relate the energy of the system to the size of the groups (based on van der Waals radii), and the distance the groups are from each other (dependent on θ).⁷⁹ From these calculations it was shown that depending on the relative sizes of R^1 and R^2 one of two conformations is favoured (**Figure 8**).

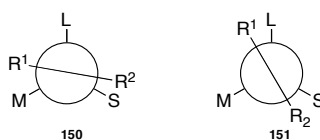
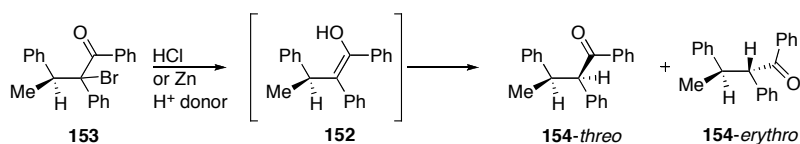


Figure 8: Calculated lowest energy conformation with $\theta = 295^\circ$ (**150**) and $\theta = 330^\circ$ (**151**)

When R^2 is much larger than R^1 **151** is calculated to be the lowest energy conformation, whilst if R^2 is only slightly larger than R^1 , **150** is the favoured conformation. Having calculated the preferred conformation of an acyclic enol

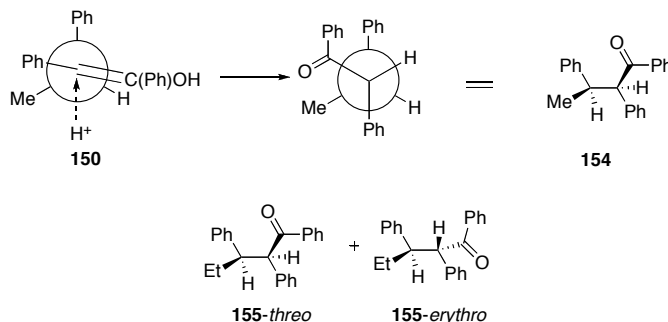
the authors attempted to rationalise experimental results using the derived theory. The first study looked at the ketonisation of enol **152**, derived from treatment of bromide **153** with either dilute acid or zinc and a proton donor to give ketone **154** (**Scheme 59**).



Scheme 59: Generation of enol **152** from bromide **153** and subsequent ketonisation

Initially the equilibrium composition of **154** was determined to consist of 40.9 % **154-threo** and 59.1 % **154-erythro** (± 2.0 %) by treatment of a pure sample of each diastereoisomer with sodium ethoxide and stirring for a 22 h period. A study of enol formation and subsequent ketonisation under a variety of conditions suggested a reoccurring theme. This was that the magnitude, but not the sense of the stereoselectivity of the ketonisation was dependent on the nature of the reaction conditions. The reactions were performed in alcoholic solvents with zinc and collidinium chloride as the proton source. All results favoured **154-threo** as the major diastereoisomer, with the more bulky alcohols giving the greatest selectivity. Although the proton source was the same in all cases (collidinium chloride) the actual proton donor is an alkyloxonium ion, thus ^tBuOH provides the greatest steric demand (82.3 % ± 1.0 % **154-threo**), whereas methanol provides the least steric demand (69.9 % ± 1.6 % **154-threo**). The authors then rationalised the results using the derived conformational analysis. When R^1 = phenyl and R^2 = C(Ph)OH the authors invoke conformation **150** as the lowest energy conformation, which correctly predicts **154-threo** as the major product (**Scheme 60**). The method was repeated with similar results on another ketone (2,3-diphenylvalerophenone, again suggested to proceed through

conformation **150**), as well as being able to correctly predict the results reported previously in the literature.⁷⁹



Scheme 60: Prediction of **154-threo** as the major diastereoisomer, and structure of 2,3-diphenylvalerophenone **155**

Houk *et al.*⁸⁰ offered another hypothesis, with similar results to those shown above. In this instance the reaction under scrutiny was the hydroboration of alkenes adjacent to a stereocentre. Once again the method initially looked at the preferred conformation of the alkene when an electrophile was approaching. The authors had previously calculated that in the hydroboration of propene the preferred conformation of the alkene is that in which the electrophile approaches from the side that is *anti*-periplanar to an allylic bond **156** (**Figure 9**).⁸¹ They proposed the reason for this lay in the unfavourable secondary orbital interaction **157** if the electrophile approaches from the same face of an allylic bond parallel to the π system. This is summarised in their own words as follows: “Attack of a reagent at an unsaturated site occurs such as to minimise antibonding secondary orbital interactions between the critical frontier molecular orbital of the reagent and those of the vicinal bond.”

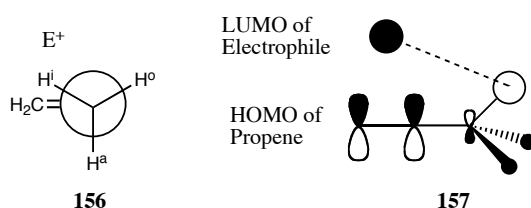


Figure 9: Newman projection showing staggered model for approach of an electrophile to propene (**156**) and the frontier orbital interaction diagram used to explain this (**157**)

Having established that the preferred conformation of the transition state is that of conformation **156**, a so-called “staggered” model, the authors next looked at cases where the substituents on the sp^3 allylic carbon were not all hydrogen. Calculations were performed replacing one of the allylic C-H bonds with a methyl group. They were able to show that the position *anti* (H^a , **156**) to the forming bond was the least demanding sterically, whilst the “inside” (H^i , **156**) position was considerably more demanding than the “outside” (H^o , **156**) position (“inside” position calculated to be almost 5 kcal/mol higher in energy than the “outside” position). Interestingly this is exactly the opposite as calculated for nucleophilic attack (attack of a hydride), where the “inside” position is lower in energy. This difference is attributed to the trajectory of the hydride sandwiching the “outside” position between the reagent and the vinylic proton, whilst in a hydroboration the “inside” position is trapped between the attacking reagent and the partial double bond. These figures (see table in **Figure 10**) imply that the preferred orientation of an allylic stereocentre in a hydroboration with a small (S), medium (M) and large (L) group is as depicted in **158**.

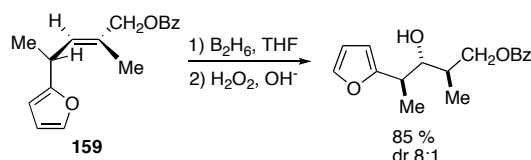
158

Methyl	H ⁻	BH ₃
Position	(kcal/mol)	(kcal/mol)
anti	0	0
outside	2.36	0.56
inside	1.03	5.41

Figure 10: Preferred conformation of an allylic stereocentre undergoing hydroboration

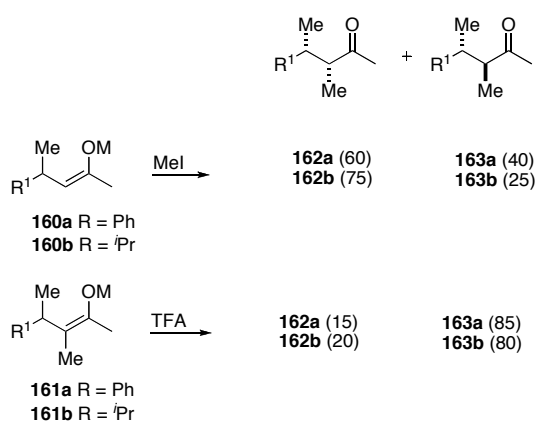
The authors of this paper note that this model is based purely on steric arguments, and in a later publication address this issue, as well as reinforcing the previously described model.⁸² The authors then demonstrated how the application of their model to literature results correctly predicts the observed diastereoselectivity for one example,⁸³ but note the levels of selectivity indicated an electronic effect enhanced the outcome. The argument presented is as follows: Placing the substituents at the allylic centre as furyl (L), methyl (M) and hydrogen (S) gives transition state **159** (**Scheme 61**), which correctly predicts the product stereochemistry; however, Houk suggests that the steric demands of a methyl and a furyl group are similar (he proposes the bulk of the furyl group can be directed away from the remaining atoms involved in the transition state), and therefore should not provide the high level of diastereoselectivity observed (~8:1). This is demonstrated by the calculation of the change in relative energy of the conformation with L = furyl, M = Me and L = Me, M = furyl for a simplified system. The energy differences are less than 0.1 kcal/mol. Instead, the authors propose that it is through space interactions of an oxygen lone-pair orbital with the alkene π -orbital. Since BH₃ is an electrophilic reagent, the double bond will become electron-deficient in the

transition state, and the interaction of the lone-pair will help to stabilise this. Thus, it is a combination of the electronic preference for the furyl to be *anti*- along with the steric preference for the methyl to be “outside” that provides the high levels of diastereoselectivity. Other researchers drew similar conclusions, and their work will be discussed later.



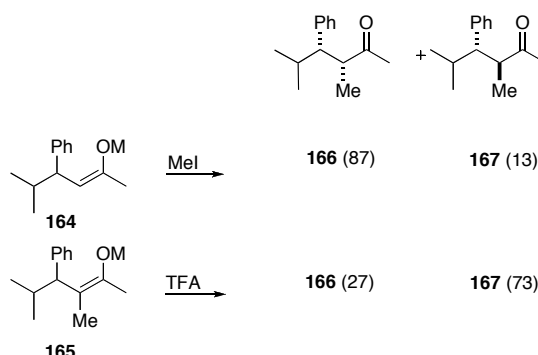
Scheme 61: Prediction of a stereochemical outcome with an electronic contribution

The next major study in the field came in a series of publications by Fleming *et al.* that detailed the results of ten years of research by the group into the diastereoselectivity of electrophilic attack on a trigonal carbon adjacent to a stereogenic centre.⁸⁴ The early work focused on the protonation or alkylation of enolates.⁸⁵ A series of enolates (generated through the conjugate addition of cuprates to the enone) were protonated or alkylated (using TFA or methyl iodide) and the ratio of products determined (**Scheme 62**).



Scheme 62: Protonation and alkylation of enolates **160** and **161**, and ratio of products **162** and

As can be seen, the results imply that the electrophilic attack occurs from the same face in the alkylation and the protonation cases (**Scheme 62**). These results correspond to the models proposed by both Zimmerman (**150**) and Houk (**158**), with S = hydrogen, M = methyl and L = Ph or *i*Pr. The ketones were deliberately equilibrated in a separate experiment to determine the thermodynamic ratio (**162a:163a** = 40:60, **162b:163b** = 65:35), which in both cases lay between the determined ratio for the alkylation and protonation, indicating that the results represented a significant degree of kinetic control. The authors suggested that enolate geometry plays little part in the diastereoselectivity, as an enolate with an *E:Z* ratio of 70:30 (**160a**) provided exactly the same result as one where the enolate ratio was 50:50. In some further experimentation the authors went on to show that the models proposed also held for phenyl ketones as well as for enolates of esters. The final experiment was concerned with enolates **164** and **165**, with the stereogenic centre now containing hydrogen, phenyl and *i*Pr group (**Scheme 63**).



Scheme 63: Protonation and alkylation of enolates **164** and **165**, and ratio of products **166** and **167**

In this case, once again the results were complementary, and indicated electrophilic attack occurred with the same sense for protonation and alkylation. The ranking of the groups on the stereogenic centre, however, is far from

unambiguous. Applying conformation **150** to the situation it is clear that the group in the large position *anti*- to the incoming electrophile is the *i*Pr group. A comparison of the *A*-values for phenyl and *i*Pr, however, show that the phenyl group is considered the larger of the two ($\text{Ph} = 2.7$, $i\text{Pr} = 2.2 \text{ kJmol}^{-1}$).⁸⁶ There is another parameter used to rank the sizing of groups, devised by Sternhell.⁸⁷ This method ranks groups by the resistance they impart to the rotation of a biphenyl derivative (**Figure 11**), and shows that an *i*Pr group can be considered larger than a phenyl group ($\text{Ph} = 1.6$, $i\text{Pr} = 2.2 \text{ \AA}$).

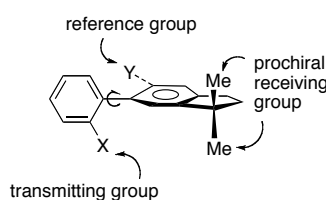
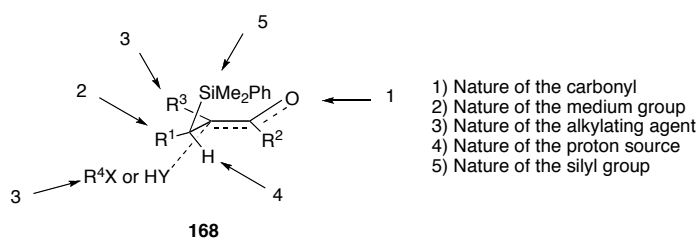


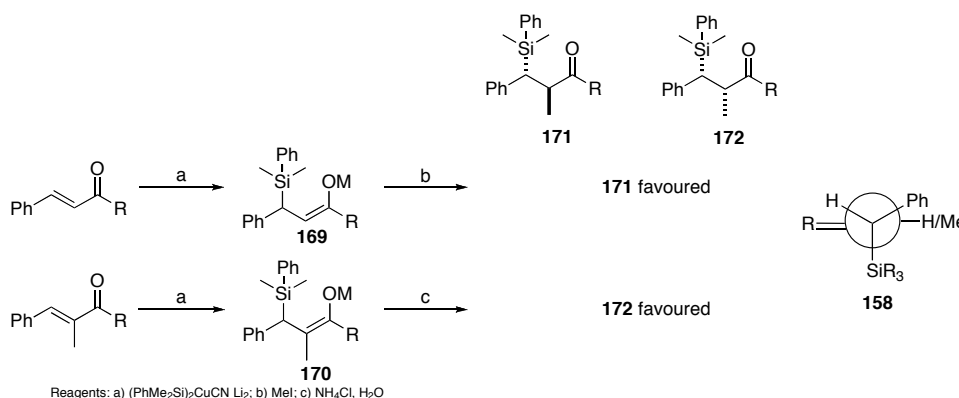
Figure 11: Depiction of the biphenyl system used by Sternhell

Another measure of size, based on the esterification of carboxylic acids,⁸⁸ is also in agreement with *i*Pr being larger than phenyl ($\text{Ph} = 0.57$, $i\text{Pr} = 0.76$). Accepting the assumption that in certain cases *i*Pr is a larger group than Ph, it would appear that the models proposed by Zimmerman and Houk can correctly predict the major product of electrophilic attack, but only when the stereocentre conformation is governed by sterics, and not electronic factors. In a second paper Fleming *et al.*⁸⁹ chose to investigate the effect of having a heteroatom on the stereocentre. The authors investigated the alkylation and protonation of enolates **168** carrying a silyl group in the β -position (**Scheme 64**).



Scheme 64: Variables to be investigated in the protonation or alkylation of β -silyl enolates

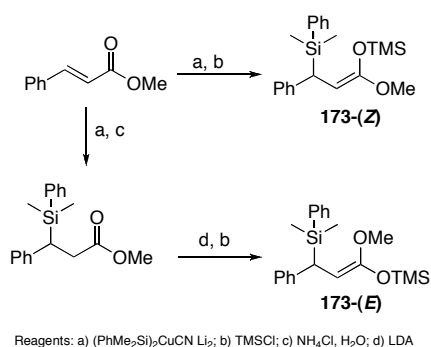
In order to assess the influence of a silyl group, a number of variables were investigated. The first variable was the nature of the carbonyl group. Enolates **169** and **170** were generated by the conjugate addition of phenyldimethylsilyl cuprate to a selection of enones (ester, aldehyde, methyl & phenyl ketones, amide, carboxylic acid and nitrile) and methylated (MeI) or protonated (NH_4Cl) accordingly (**Scheme 65**).



Scheme 65: Investigation into effect of enolate on diastereoselectivity

In all cases it was shown that alkylation and protonation occurred from the same face, and the model **158** once again applied, with the silyl group occupying the large (*anti*-) position, phenyl as the medium (outside) position and the proton occupying the small (inside) position. The selectivities of the alkylations were

much higher than observed in the absence of the silyl group for the ester, aldehyde, methyl ketone and amides (92:8 - >98:2), however, much lower for the carboxylic acid and nitrile. These discrepancies are ascribed to the absence of large amounts of allylic 1,3 strain in the transition state lowering the energy of the alternate transition state. This is a valid argument for the nitrile, however, in the case of the carboxylic acid, an oxylithium group is similar in size to a proton (*i.e.* an aldehyde) and this example showed good selectivity. The phenyl ketone underwent a 1,4-silyl transfer (Brook rearrangement) and the resultant enol-ether was isolated. The protonation series provided uniformly high diastereoselectivities (including the nitrile case, the carboxylic acid reaction was not carried out) with the exception of the previously mentioned phenyl ketone case, where the Brook rearrangement was again observed. In a further experiment the effect of enolate geometry was explored. Generation of (*E*) and (*Z*) TMS-enol ethers **173** and subsequent quenching with MeI provided the same ratio of products (97:3) in both cases, an indication that enolate geometry played little part in the diastereoselectivity (**Scheme 66**).



Scheme 66: Investigation into enolate geometry

More importantly this experiment ruled out the possibility that the oxyanion is co-ordinated to the β -silyl group creating cyclic intermediate **174** (**Figure 12**). Alkylation from the less hindered top face of **174** would predict the same major

product as predicted by Houk's conformer **158**. As this co-ordination is only possible for the (*Z*)-enolate (**173-(Z)**), and high diastereoselectivity is observed with the (*E*)-enolate (**173-(E)**), the results are only compatible with an open-chain stereochemical model as proposed.

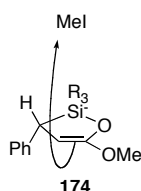
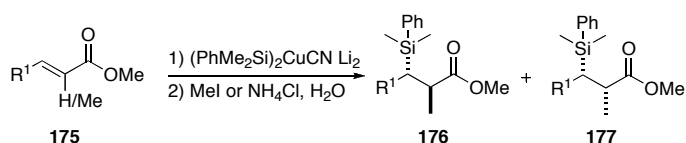


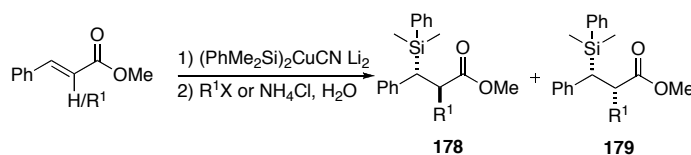
Figure 12: Discounted cyclic intermediate

The authors next chose to vary the medium sized group (R^1 , **Scheme 64**). Following similar lines as before, a number of ester enolates were generated by the addition of a silyl-cuprate to the α,β -unsaturated ester **175** followed by protonation or alkylation. The results for methylation (**Table 1**) show that, with the exception of the phenyl, the diastereoselectivity falls with an increase in steric bulk (according to the relative *A*-values) of the medium group. As was noted earlier *A*-values are not the only parameter available to compare steric hinderance, and comparison of Sternhell's parameter places phenyl as smaller than a methyl ($\text{Ph} = 1.6$, $\text{Me} = 1.8$ Å), and the ranking follows the methylation ratio observed. As both Sternhell's parameter and *A*-values rank a silyl group ($\text{TMS } A\text{-value} = 2.5 \text{ kJmol}^{-1}$, Sternhell's parameter = 2.1 Å) as smaller than a *t*Bu group the authors propose that this implies the existence of an electronic component to the diastereoselectivity. In this instance the protonation series again provides protonation from the same face as the alkylation, but with the selectivity increasing with increasing steric bulk of the medium group.

Table 1: Variation of medium sized group

R ¹	Ratio 176:177 methylation	Ratio 176:177 protonation
Ph	97:3	15:85
Me	91:9	13:87
<i>i</i> Pr	85:15	4:96
<i>t</i> Bu	66:34	4:96

The next variable to come under scrutiny was the effect of varying the alkylating agent. Once again a number of enolates were alkylated or protonated and the ratio of diastereoisomers recorded (**Table 2**). Again the alkylations provided excellent levels of stereocontrol in agreement with the proposed model for a wide range of electrophiles. In contrast, the protonation reactions proved to be relatively unselective. Low diastereoselectivities were seen in many cases, and the reactions did not always favour **179** as the major isomer (**Table 2**, entries 4 and 5)

Table 2: Variation of alkylating agent

Entry	R ¹	X	Ratio 178:179	Ratio 178:179
			Alkylation	protonation
1	Me	I	97:3	15:85
2	Et	I	95:5	20:80
3	Bu	I	94:6	27:73
4	<i>i</i> Pr	I	95:5	60:40
5	PhCH ₂	Br	97:3	71:29
6	CH ₂ =CHCH ₂	Br	95:5	31:69
7	MeO ₂ CCH ₂	Br	98:2	10:90

The reason the protonation reactions are much less selective and unpredictable than their alkylation counterparts lies in the differences in the arrangement of the groups with respect to the incoming electrophile and the enolate (**Figure 13**). Conformation **180** has the three differently sized groups arranged as before, with the electrophile attacking *anti*- to the large group. The small group occupies the sterically more demanding inside position, whilst the medium group takes the less hindered outside position. In the previous examples the groups on the nucleophilic centre of the enolate were either a methyl or a proton, so there was only a small steric clash between this group and the outside position (effectively minimising 1,3-allylic strain would seem to be more important than minimising 1,2-allylic strain). In **Table 2** the group on the nucleophilic centre of the enolate is much larger than a methyl, and this makes the relative energy difference between conformation **180** and conformation **181**, which minimises 1,2-allylic

strain over 1,3-allylic strain by placing the medium group in the inside position, much smaller, and thus reduces the diastereoselectivity.

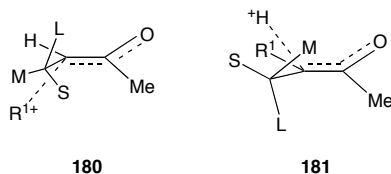


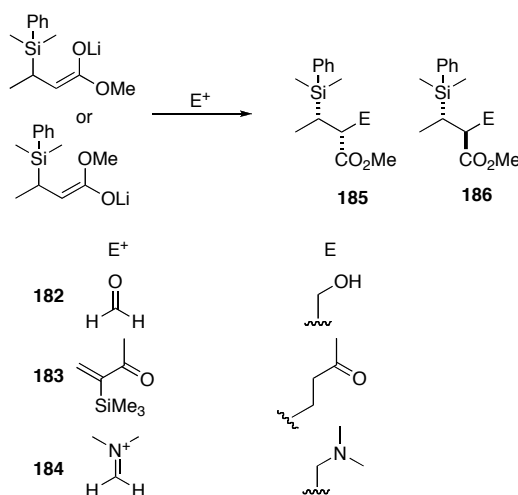
Figure 13: Conformations with a proton (**180**) and a larger group (**181**) on the nucleophilic centre of the enolate

The authors also looked at the effect of varying the proton source and the silyl group, but these results were inconclusive and will not be covered in this review. The results of this paper would suggest that having a stereocentre with a silicon substituent increases the magnitude of the diastereoselectivity without affecting the sense. The authors argue that the magnitude of the diastereoselectivity is due to a combination of the large size of a silyl group and an electronic effect that operates to reinforce the diastereoselectivity. The authors also note that there is only marginal evidence for an electronic effect, depending upon whether one regards a silyl group as bigger sterically than a *t*Bu group or not (whilst a silyl group obviously possesses a large steric bulk, the longer silicon-carbon bond places this bulk further from the site of reaction).

The final paper of interest in this series concerns the reaction of open-chain enolates carrying a silyl-containing stereocentre with trigonal electrophiles.⁹⁰ The authors first established that replacing an alkylating agent with a simple trigonal electrophile, such as formaldehyde **182**, methyl vinyl ketone **183** or Eschenmoser's salt **184** did not affect the diastereoselectivity (**Table 3**). In all cases the major isomer of the product was **185** with excellent diastereoselectivity. This again equates to attack of the electrophile *anti*- to the

large (silicon) group, with the medium (methyl) group occupying the outside position.

Table 3: The use of simple trigonal electrophiles



E^+	Ratio 185:186 (<i>E</i> -enolate)	Ratio 185:186 (<i>Z</i> -enolate)
182	71:29	81:19
183	93:7	91:9
184	87:13	82:18

As shown in **Table 3**, the enolate geometry plays only a small role in the diastereoselectivity across these two centres, although the expected aldol stereochemistry is seen when more complex aldehydes resulting in a third stereocentre are used (*i.e.* *E*-enolates provide the *anti*-aldol products and the *Z*-enolate provides the *syn*-aldol products). Finally the authors show that the reaction proceeds with the same sense of diastereoselectivity if the *E*- and *Z*-silyl enol ethers are used in place of the metallated enolates.

Although the work of Fleming *et al.* predominantly makes use of a silyl group on the stereocentre, the model they propose can also be applied to an all carbon based stereocentre. Whilst investigating iodoacetoxylation of a steroidal system Barton *et al.*⁹¹ observed high levels of diastereoselectivity for the electrophilic addition of a number of reagents to the 22-23 bond of 3 α ,5 α -cycloergosta-7,22-dien-6-one **187** (Figure 14).

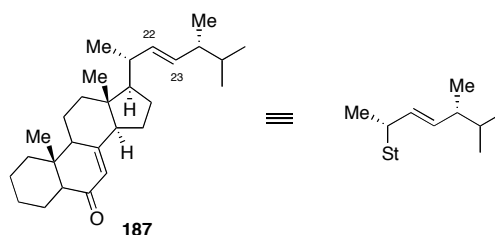
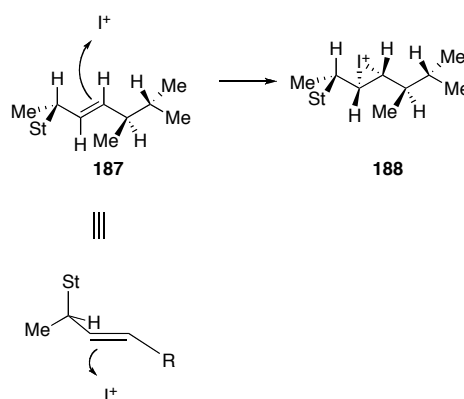


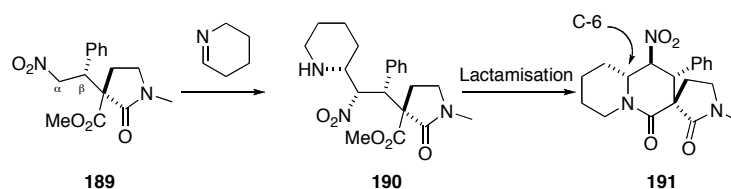
Figure 14: Structure of 3 α ,5 α -cycloergosta-7,22-dien-6-one **187**

The authors noticed that upon treatment with a number of reagents, the electrophilic addition proceeded to give one diastereoisomer as the major product in each case. If the model proposed by Fleming is applied to the system, with the steroidal (St) side chain taking the position *anti*- to the incoming electrophile (I^+ in this case) and the methyl group in the outside position the correct stereochemistry is predicted (Scheme 67).



Scheme 67: Application of Fleming's model to a steroidal system

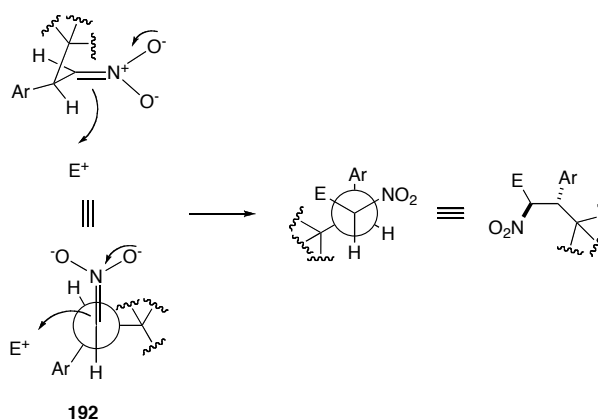
This review of the literature suggests that a given system will obey a general rule, provided that the substituents about the proximal stereocentre can be readily distinguished by their steric demand. The large group always takes a position orthogonal to the π -system. The small group (usually a proton) occupies the sterically more congested inside position, and the medium group thus lies in the less congested outside position. The approach of the electrophile then comes from the less hindered face, *anti*- to the large group. In this final section we will attempt to apply these rules to a literature example of a nitro-Mannich reaction with an α -stereocentre, in order to see if they can correctly predict the stereochemical outcome. To the best of our knowledge there is only one set of this type of system being used within a nitro-Mannich context. These are the examples developed by Dixon *et al.* (**Scheme 27**, **Scheme 28** and **Scheme 36**), and are all closely related. The general reaction scheme can be depicted as follows (**Scheme 68**). The nitronate that takes part in the nitro-Mannich step is generated from nitro-alkane **189**. Subsequent nitro-Mannich reaction furnishes β -nitroamines of the type **190** (only one example shown). Ensuing lactamisation provides fused bicycle **191**. In all the examples the reaction gives the depicted diastereoisomer as the major product, in very high selectivity.



Scheme 68: Depiction of generalised reaction scheme of Dixon *et al.*³⁴

The substituents on the β -stereocentre are an aromatic group, a proton and a 1,3-dicarbonyl group. Approximating the latter to either an isopropyl or a tertiary butyl group, and assuming these to be larger than the aromatic group (based on

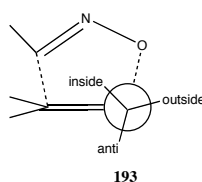
Sternhell's parameter, $^t\text{Bu} = 3.6$, $^i\text{Pr} = 2.2$, $\text{Ph} = 1.6 \text{ \AA}$), we predict that the reactive conformation should resemble **192** (**Scheme 69**), by analogy to the enolate studies of Fleming. The large group is *anti*- to the approaching electrophile, the sterically more demanding inside position is occupied by the small group, in this case a proton, and the aromatic group lies in the outside position. If the reaction is followed through we see that the observed stereochemistry (**Scheme 68**) is not the same as that predicted by the model.



Scheme 69: Predicted reactive conformation **192** and resultant stereochemistry

There is, of course, the possibility that the reaction is controlled by electronic factors rather than sterics, or a combination of both. The literature pertaining to the effect an adjacent heteroatom containing chiral centre has on the diastereoselectivity of electrophilic attack is limited. The previous section described the work of Fleming *et al*, whose work concentrated on stereocentres containing a silyl group. They were able to show that in this case, the diastereoselectivity was due to a combination of a preference for the large silyl group to reside in the *anti*-position for steric effects, combined with an electronic effect, whereby the most electropositive substituent prefers to be in the *anti*-position. This preference for the electropositive group to be *anti*- allows for the

maximisation of electron donation from the $\sigma_{\text{C-D}}$ (carbon-donor atom bond) into the transition states LUMO (developing $\sigma^*_{\text{C-E}}$ orbital). The outside position is the second favoured position, and the inside is least favoured, as the $\sigma_{\text{C-D}}$ overlap with the LUMO is negligible. Conversely, Houk *et al.*⁹² have looked at the effect of having an electronegative heteroatom, specifically an alcohol, on the stereocentre. The group looked at the stereoselectivity of nitrile oxide cycloadditions to allyl alcohol **193** (Figure 15).



Position	Me	OH	OMe
	(kcal/mol)	(kcal/mol)	(kcal/mol)
anti	0.0	4.9	0.7
inside	1.1	0.8	0.0
outside	0.6	0.0	2.9

Figure 15: Preferred conformations of but-1-ene and allyl alcohol undergoing nitrile oxide cycloaddition

As can be seen the values for the methyl group follow the previously explained model, where the least sterically demanding position is *anti*-, the inside position is the most sterically demanding, and the outside position is intermediate. The values for allyl alcohol show that the *anti*-position is greatly disfavoured over the inside and outside positions, but the outside position is slightly favoured over the inside. The authors attribute this preference for the alcohol in the outside position to allow for maximised hydrogen bonding to the nitrile oxide. If the

calculations were modified to include a hydrogen bond acceptor as solvent, or looked at the allylic methyl ether, the inside position was favoured over the outside. This is rationalised by the same argument used by Fleming, in that withdrawing electron density will destabilise the transition state, and donating electron density will stabilise the transition state. Placing an electronegative substituent *anti*- will maximise the electron withdrawing interaction, and thus maximises the destabilisation. Placing the electron withdrawing substituent in the inside position minimises the $\sigma^* \pi$ overlap, and allows for the electron donating σ_{CH} or σ_{CR} orbitals to have maximum overlap with the π orbital, and help stabilise the transition state.

Another factor to be considered when taking electronic factors into account is the symmetry of the double bond. Enolates, and nitronates, have highly polarised double bonds due to the presence of electronegative elements. Houk *et al.*⁹² has calculated that this affects the trajectory of the incoming electrophile, and thus can affect which position, the inside or the outside, is more crowded. When the angle of trajectory is obtuse (*i.e.* when the double bond is polarised) the outside position possesses the greater steric demand, and the medium group prefers the inside position (*cf.* Felkin-Anh model). They also state that this “outside-crowded” model **194** will probably be in effect for reactions with 5- and 6-membered transition states (**Figure 16**).⁹²

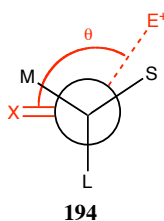
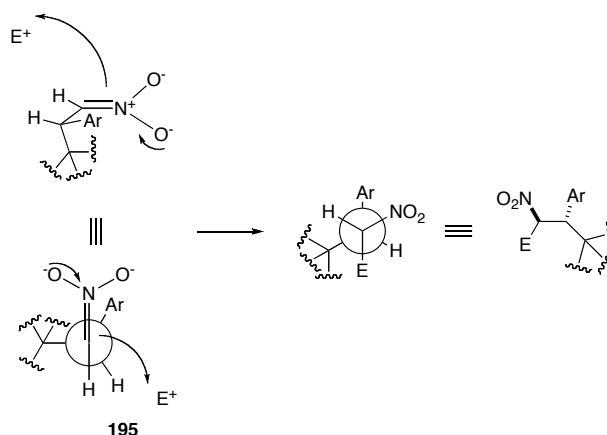


Figure 16: “Outside-crowded” model proposed by Houk for reactions involving heavily polarised bonds or cyclic transition states

If we return to the nitro-Mannich case, we can now modify the model for the work of Dixon to include electronic factors. As a nitronate possesses a highly polarised double bond, and the reaction is often presumed to proceed through a Zimmerman-Traxler transition state, it is fair to invoke Houk's "outside crowded" model **194**. At this point we are assuming any electronic factor due to orbital mixing will be negligible in the absence of any heteroatoms directly bonded to the allylic carbon atom. So, the large 1,3-dicarbonyl group again takes a position *anti*- to the incoming electrophile, which, now attacking at a more obtuse angle, makes the least hindered position inside, with the hydrogen outside lying close to the trajectory of the electrophile (**Scheme 70**). In this case, if the model is followed through the predicted stereochemistry is in agreement with the experimentally observed diastereoselectivity (**Scheme 68**). Whilst this model would seem to predict the correct stereochemistry, it is possible that other factors control the diastereoselectivity, and the authors point out that the diastereoisomer observed is able to place all the substituents of the lactam ring in an equatorial position, and thus it is the rate of the irreversible lactamisation that controls the diastereoselectivity, and that the nitro-Mannich step is unselective and reversible.



Scheme 70: Application of Houk's outside crowded model to a nitro-Mannich system

In the previous sections we have presented a review of the nitro-Mannich literature, encompassing the discovery and early work up to the more recent developments. Although the nitro-Mannich reaction has seen considerable improvements in the recent past, we still believe the reaction has major flaws. A close look at the review shows that the large majority of protocols only use nitromethane, or higher homologue, commercially available nitroalkanes. This represents a major limitation for the reaction, and perhaps explains why the reaction has been rarely employed within a complex natural product synthesis. The next section briefly reviewed the general area of nucleophilic additions to nitro-alkenes, the most versatile method for the synthesis of more complex nitroalkanes. The final section discussed the literature pertaining to the stereoselectivity of electrophilic attack on a trigonal carbon adjacent to a stereocentre. Having shown that a number of general rules exist, depending on the nature of the reaction, we applied these rules to a nitro-Mannich system with some success. With this literature precedent we hope that we can explain the results obtained from our research using these principles. How these subjects relate to the research carried out will be explained in the following section.

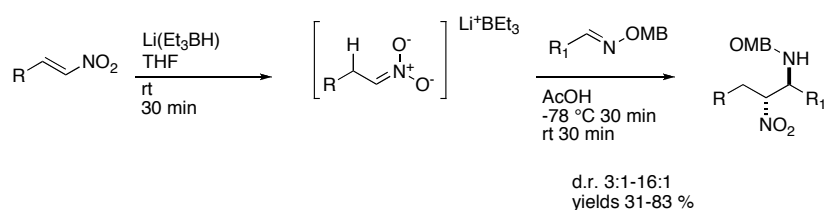
Chapter 2:

Results & Discussion

Results and Discussion

2.1 Proposed Research

As was stated in the introduction, the nitro group is a wonderfully versatile functional group. The introduction also explored two areas of research pertaining to the chemistry of this group, that is the addition of nucleophiles to conjugated nitro-alkenes, and the nitro-Mannich reaction. These two reactions can produce a wide variety of structures efficiently, however, the aim of this research is to couple these two methods to provide much greater complexity in a single step. Previous research within the group (**Scheme 71**),⁹³ and some recently published procedures (see section 1.2.8) has shown that this is indeed possible, and is a powerful tool for the synthesis of complex, poly functionalised structures in a single step. We have been able to show that nitronates generated *in-situ* by the addition of a hydride to a nitro-alkene can successfully be trapped by imines. The yields were moderate to high for a range of substrates and good to excellent diastereoselectivity was observed.



Scheme 71: A reductive 1,4 addition/nitro-Mannich reaction

Having achieved a reductive 1,4-addition/nitro-Mannich reaction, it was now our aim to further explore the boundaries of this methodology by the use of a more complex nucleophile. If this methodology proved to be successful we would be

able to set up three contiguous stereocentres and form two carbon-carbon bonds in a single reaction vessel. From the point of view of efficiency this represents a major step forward. The following sections will discuss the results obtained towards this goal.

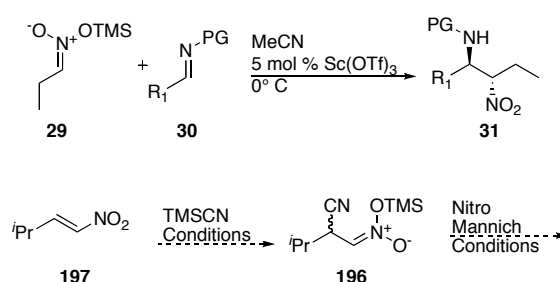
2.2 Cyanide Addition

2.2.1 Overview

We have shown that the desired 1,4 addition/nitro-Mannich reaction is possible with a simple nucleophile, a hydride (**Scheme 71**). We now desired to expand the scope of this reaction with the use of a more complex nucleophile. With the aim of incorporating as much orthogonal functionality as possible we decided to investigate the addition of cyanide. The product would then contain three separate nitrogen-containing groups with differing reactivity. The nitrile group itself is a highly flexible functionality, and can be manipulated in many ways. When combined with the β -nitro-amine provided by a nitro-Mannich reaction the potential products become extremely versatile synthetic building blocks. The only literature precedent for the addition of a cyanide ion to a nitro-alkene was an isolated example reported by Barton *et al.*⁷¹ This procedure uses NaCN and acid, which we thought would be incompatible with a one pot conjugate addition/nitro-Mannich reaction because of the potential of nitronate protonation prior to imine addition. With this in mind, and wishing to avoid the use of acidic conditions if possible, initial work looked at the development of a new method for the addition of cyanide to conjugated nitro-alkenes.

2.2.2 Trimethylsilyl Cyanide

The first reagent chosen for investigation was trimethylsilyl cyanide (TMSCN). Less toxic than the inorganic counter-parts, it is a stable liquid, known to be a source of cyanide.⁹⁴ The reagent was chosen as the intermediate **196** (**Scheme 72**) that could be formed bears a striking similarity to the TMS-nitronates **29** employed by the group in a previous nitro-Mannich protocol.¹⁸

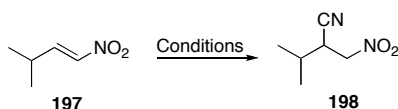


Scheme 72: TMS-nitronate nitro-Mannich protocol and proposed TMSCN addition/nitro-Mannich reaction

Nitro-alkene **197** (**Scheme 72**) was chosen as the substrate for optimisation as it provided a simple NMR spectrum for quick analysis of reaction conditions. Literature precedent had shown that TMSCN adds to unsaturated carbonyl compounds in the presence of a Lewis acid.⁹⁵ Under the conditions reported, that is three equivalents of TMSCN (also acting as the solvent) and 10 mol % ZnI_2 , no reaction was observed, even upon prolonged reaction times. A variety of different conditions were attempted (**Table 4**), however no reaction was seen to occur. The addition of toluene and gentle heating again resulted in no reaction, and extended heating at reflux gave degradation of the starting material. An increase to a stoichiometric amount of the Lewis acid again led to degradation.

Replacement of the ZnI_2 with other Lewis acidic reagents resulted in either no reaction (TMSOTf) or degradation (AlEt_3 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$).

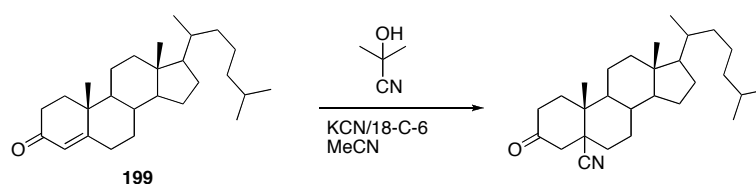
Table 4: Attempted optimisation of TMSCN conditions^a



Entry	Lewis Acid	Time (h)	Temp/ °C	Result
1	ZnI_2	48	20	s.m.
2	ZnI_2	16	60	s.m.
3	ZnI_2	16	80	s.m.
4	ZnI_2	48	110	degradation
5	ZnI_2 (1 eq)	48	20	s.m.
6	AlEt_3	48	20	degradation
7	TMSOTf	16	80	s.m.
8	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	48	20	degradation

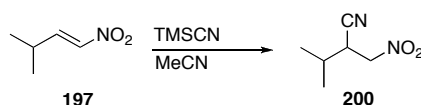
^a All reactions performed on nitro-alkene **197**, with three eq. TMSCN and 10 mol % Lewis acid, unless otherwise noted.

With no positive results from the combination of TMSCN and a Lewis acid, a different approach was investigated. Liotta *et al.* had reported the addition of cyanide to a steroidal unsaturated ketone **199** using acetone cyanohydrin and a catalytic amount of KCN/18-crown-6 (**Scheme 73**).⁹⁶ In the absence of either KCN or 18-crown-6 no reaction was observed, perhaps an indication that a catalytic amount of cyanide is required for the reaction to proceed.



Scheme 73: Addition of “naked cyanide” to unsaturated ketone **199**

It was decided to test whether a source of cyanide was needed to start the TMSCN reaction. Submitting nitro-alkene **197** to the same conditions (**Table 4**), but with 10 mol % KCN/18-crown-6 in acetonitrile, resulted in an encouraging 5:1 ratio of nitro-alkene **197**: β -nitronitrile **200**. Although the result is greatly in favour of the starting material, a 5:1 ratio does imply that KCN/18-crown-6 is acting as a catalyst, although with a very low turnover number (*ca* 1.7). Once again a variety of conditions were tried to improve this ratio in favour of the product, however this could not be achieved (**Table 5**).

Table 5: Attempted optimisation of TMSCN, KCN/18-crown-6 conditions^a

Entry	eq. KCN/18-C-6	Lewis acid (0.1 eq)	Time (h)	Temp / °C	Result ^b 197:200
1	0.1	ZnI ₂	48	20	5:1
2	0.1	-	48	20	1:0
3	0.5	ZnI ₂	48	20	5:1
4	1	ZnI ₂	48	20	5:1
5	1	-	48	20	5:1
6 ^c	1	-	48	20	1:0
7 ^d	0.1	ZnI ₂	72	20	5:1
8	0.1	ZnI ₂	24	80	degradation
9	0.1	ZnI ₂	48	-40	>10:1
10	0.1	ZnI ₂	16	-40	>10:1
11	0.1	TMSOTf	72	20	>10:1
12	0.1	BF ₃ .Et ₂ O	24	20	degradation

^a All reactions performed on nitro-alkene **197**, with 3 eq. TMSCN in acetonitrile, unless otherwise indicated.

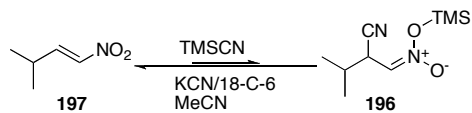
^b Analysis of crude ¹H NMR, comparison of integrations of vinylic proton (6.95 ppm) and CH₂NO₂ protons (4.57 ppm).

^c Reaction performed in the absence of TMSCN.

^d Reaction performed with 10 eq. of TMSCN.

Interestingly, in the absence of TMSCN no reaction was observed, even with a stoichiometric amount of KCN/18-crown-6. Changes in temperature, reaction time and Lewis acid again had little effect, the only observable difference being a slight decrease of the ratio in favour of nitro-alkene **197** (>10:1). Strangely, increases in the number of equivalents of TMSCN or KCN/18-crown-6 again failed to alter the extent of the reaction. We believe this is due to the nature of the cyanide as both a nucleophile, and a good leaving group. The starting

material could be reforming through a simple E₁CB elimination and the observed ratio reflects the thermodynamic position of the equilibrium (**Scheme 74**).

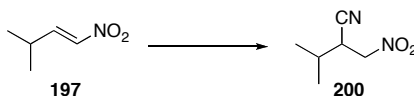


Scheme 74: Equilibrium between nitro-alkene **197** and intermediate **196**

2.2.3 Acetone Cyanohydrin

With little progress towards the desired aim using TMSCN it was decided to look at an alternative cyanide source. Following on from the favourable result gained from the use of catalytic KCN/18-crown-6 in combination with a stoichiometric cyanide source (**Table 5**), attention shifted to acetone cyanohydrin. Treatment of nitro-alkene **197** with 1.2 eq acetone cyanohydrin and 10 mol % KCN/18-crown-6 in acetonitrile resulted in complete consumption of the starting material in two hours, to give **200** in 72 % isolated yield. In an attempt to improve this result an optimisation procedure was attempted, focusing on solvent, equivalents of acetone cyanohydrin and time (**Table 6**).

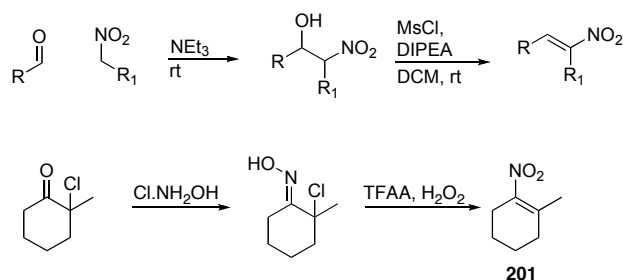
Table 6: Solvent screen and acetone cyanohydrin optimisation



Entry	Solvent	Cyanohydrin eq	Time (h)	Yield (%)
1	MeCN	1.2	2	72
2	MeCN	2.4	2	70
3	MeCN	1.2	48	44
4	THF	1.2	24	38
5	Toluene	1.2	2	44
6	DCM	1.2	2	72

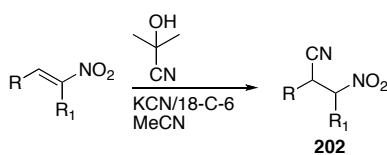
As can be seen a greater excess of cyanohydrin had no effect on the yield. A prolonged reaction time leads to a much lower yield, presumably due to degradation of the product under the reaction conditions. The initial solvent

choice was shown to be the most efficient, along with DCM. The reaction in THF was much slower, taking 24 h to reach completion, and along with toluene showed significantly lower yields. As acetonitrile was the solvent reported in the literature for the addition to α,β -unsaturated carbonyls, we decided to use this as the solvent. Having fully optimised the reaction conditions for nitro-alkene **197** the scope of the reaction was investigated. A range of nitro-alkenes were synthesised by the Et₃N catalysed Henry reaction of nitromethane/propane,⁹⁷ followed by dehydration using MsCl and DIPEA (**Scheme 75**).⁹⁸ The exception to this was nitro-alkene **201** (entry 8, **Table 7**), which was synthesised from 2-chloro-2-methylcyclohexanone,⁹⁹ *via* oxidation of the corresponding oxime (**Scheme 75**).¹⁰⁰ The *E* geometry of tri-substituted nitro-alkenes as described in the literature is based on ¹H NMR shifts of the vinylic proton (~7 ppm as compared with ~6 ppm for *Z*).



Scheme 75: Synthesis of nitro-alkenes

As can be seen good yields were obtained for all the examples. The reaction tolerates mono-, di- and tri-substituted nitro-alkenes, hindered substrates (entry 6) and functionalisation (entry 7). In the cases of entries 2 and 5 the reaction was not diastereoselective, the products being isolated as a separable 1:1 mixture. The product resulting from entry 8, however, was isolated as a single diastereoisomer **202-h**.

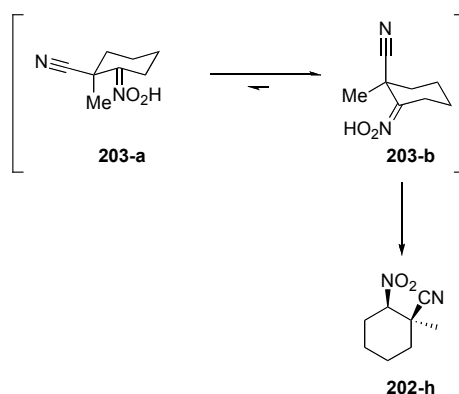
Table 7: Substrate scope^a

Entry	Product	R	R ₁	Reaction time (h)	Yield (%)
1	202-a	<i>i</i> Pr	H	3	73
2	202-b	<i>i</i> Pr	Et	3	76
3	202-c	Cy	H	3	76
4	202-d	<i>n</i> Pentyl	H	17	68 ^b
5	202-e	<i>n</i> Pentyl	Et	17	71 ^b
6	202-f	<i>t</i> Bu	H	5	64
7	202-g	TBDPSiOCH ₂ CH ₂	H	17	76 ^b
8	202-h			12	84

^a All reactions carried out with 1.2 eq acetone cyanohydrin, 10 mol % KCN/18-C-6 in MeCN at rt unless otherwise noted.

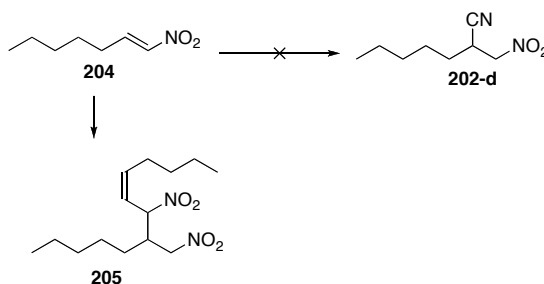
^b Nitro-alkene added via syringe pump over a 5 h period to acetone cyanohydrin, 18-C-6 and KCN in MeCN followed by a further addition of acetone cyanohydrin (1.2 eq) after addition was complete.

The relative stereochemistry of **202-h** was confirmed by single crystal x-ray diffraction to be the *syn*-isomer. Presumably this selectivity arises through tautomerisation of the thermodynamically more stable chair form **203-b** of the nitronic acid to give the equatorial nitro function (*A*-values of CN = 0.84 kJmol⁻¹ vs. CH₃ = 7.28 kJmol⁻¹).¹⁰¹



Scheme 76: Proposed mechanism for formation of **202-h**

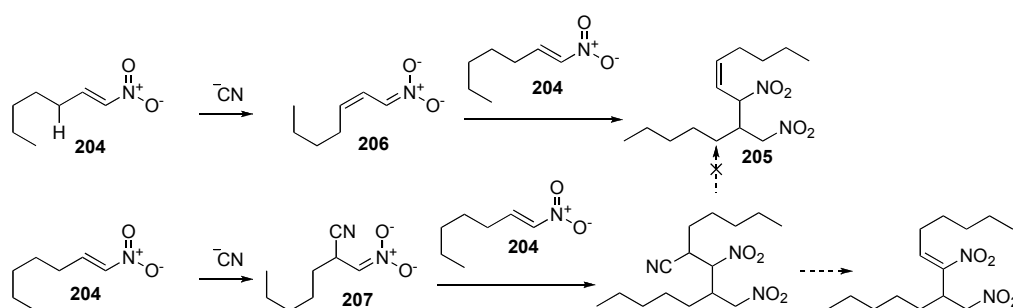
During the initial experimentation, it was found that under the optimised conditions nitro-alkene **204** (Table 7, entry 4, R = *n*-pentyl, R¹ = H) did not react as expected, and the desired β -nitronitrile **202-d** was not isolated. Instead an unwanted by-product was formed (Scheme 77). Analysis of the spectral data showed the by-product to be **205** (23 % isolated yield).



Scheme 77: Reaction of **204** under the optimised condition

A plausible mechanism for the formation of **205** could be conjugate deprotonation of one molecule of **204** by cyanide ion to give nitronate **206**, followed by conjugate addition of this nitronate to another molecule of the starting material (Scheme 78). The alternative mechanism, conjugate addition of nitronate **207**, resulting from conjugate addition of cyanide to the starting

material, followed by elimination of HCN can probably be discounted as the alkene in **205** is not in conjugation with the nitro group, as would be expected through the elimination of HCN. In addition, when the reaction of nitro-alkene **197** was scaled up a similar by-product was observed in a much lower yield (3 %). The more hindered nature of the allylic proton would make this deprotonation more difficult on steric grounds, accounting for the much lower yield. The assignment of *cis* alkene geometry was derived from the ^1H NMR coupling constant ($J = 10$ Hz), but the reason why the thermodynamically less stable alkene geometry is observed is unknown.

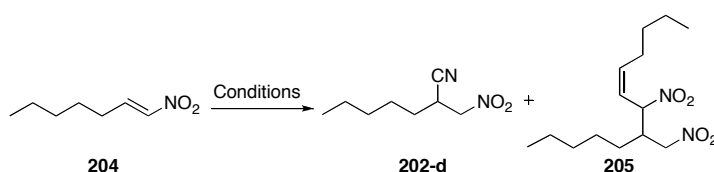


Scheme 78: Proposed mechanism of formation of **205**, and alternate discounted mechanism

In order to discount the possibility of misassignment of the geometry based on the coupling constant a review of all literature compounds displaying the non-conjugated nitro-alkene functionality was undertaken. Of the compounds found displaying this motif in the literature only 30 have the data reported and have a defined multiplet for the vinylic protons. Eleven of the compounds display *cis*-relationships, the remaining 19 being *trans*- (see appendix A for further details). The range of J values for the *cis*- compounds are 10.0-12.6, whilst the values for the *trans*-compounds lie in the region 15.3-16.4. This would imply our assignment as the *cis*-isomer is indeed correct.

In order to avoid this unwanted side reaction alternate reaction conditions were trialled. Dilution of the reaction by ten-fold resulted in a much longer reaction time (4 days), but with no significant reduction of dimer formation. Reverse and slow addition (1 h by syringe pump) of the nitro-alkene to the mixture of KCN, 18-C-6 and acetone cyanohydrin decreased dimer formation (18 %), and the desired β -nitronitrile was isolated in 41 % yield. Increasing the addition time to 5 hours halted dimer formation completely, and addition of a further 1.2 eq of acetone cyanohydrin after the syringe pump addition raised the isolated yield of the product from 59 % to 68 %.

Table 8: Optimisation for formation of β -nitronitrile **202-d**

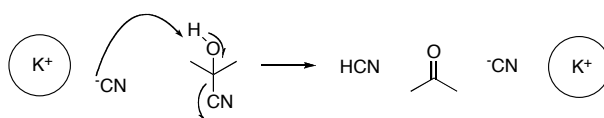


Entry	Addition time (h)	Cyanohydrin eq	% 202-h	% 205
1	1	1.2	41	18
2	5	1.2	59 ^a	0
3	5	1.2 + 1.2 ^b	68	0

^a 13 % starting material recovered

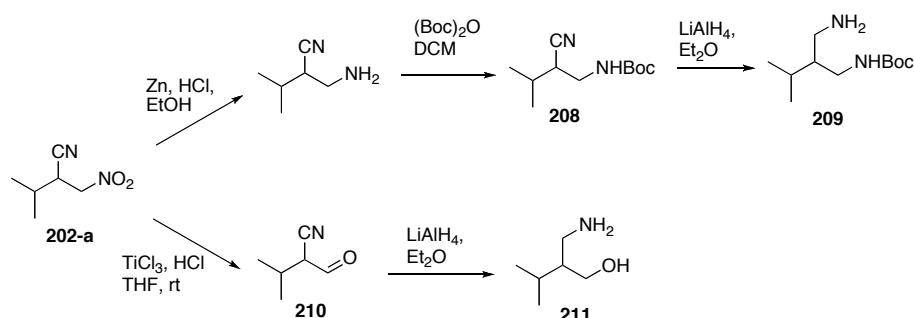
^b 1.2 eq. added at start of reaction and further 1.2 eq added after 5 h addition.

In order to gain some insight into the general mechanism for the hydrocyanation of nitro-alkenes, control reactions were performed in the absence of 18-crown-6 or acetone cyanohydrin and in the absence of both 18-crown-6 and KCN. In all cases no reaction was found to occur. This indicates the *in situ* generated HCN, formed from the cyanide anion abstracting a proton from the acetone cyanohydrin (which decays into acetone, regenerating the cyanide anion, **Scheme 79**) is important for the reaction to proceed.



Scheme 79: Generation of HCN from 18-crown-6/KCN and acetone cyanohydrin

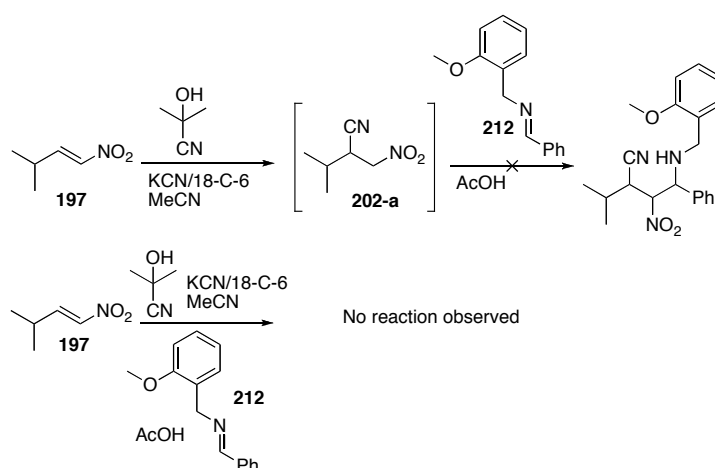
Having synthesised a number of β -nitronitriles it was decided to demonstrate the utility of these products as versatile building blocks by investigating functional group interconversions on β -nitronitrile **202-a** (**Scheme 80**). The nitro group was reduced with Zn/HCl, and the crude material Boc protected to give the *N*-Boc protected β -aminonitrile **208** in 79 % over the two steps. Reduction with LiAlH_4 in refluxing Et_2O gave mono-protected diamine **209** in 89 %. It is interesting to note that this product would be difficult to obtain from mono-protection of the parent symmetrical 1,3-diamine. Alternatively Nef reduction of **202-a** with acidic Titanium (III) chloride provided unstable α -cyano-aldehyde **210**. The crude aldehyde **210** was immediately treated with LiAlH_4 to give γ -amino-alcohol **211**, isolated in 64 % yield from **202-a** after ion exchange chromatography. Amino-alcohol **211** is a literature compound,¹⁰² synthesised in very low yields (8 % from 3-*iso*-propylglutaric acid) over seven steps. Our route provides **211** in 43 % from *iso*-butyraldehyde, in only five steps, further highlighting the synthetic utility of this reaction.



Scheme 80: Functional group interconversions of **202-a**

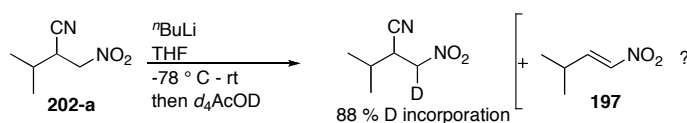
2.2.3.1 Towards a One-Pot 1,4-Addition/Nitro-Mannich Reaction

Having fully developed the 1,4-addition methodology focus shifted to incorporating this into a one-pot strategy. Initially the addition of cyanide to nitro-alkene **197** was performed in the standard manner, however, when the reaction had reached completion a solution of imine **212** and acetic acid was added, and the reaction monitored by NMR at various time points. At no point during the reaction (up to 24 h) were any nitro-Mannich like products observed. In fact the only species present were the 1,4-addition product **202-a**, and imine **212**. Presumably the acidic HCN formed not only undergoes the 1,4-addition, but also protonates the nitronate, thus rendering it unable to react in the nitro-Mannich step. In an attempt to by-pass this, the reaction conditions were altered, so the imine and acetic acid were present along with all the other reagents at the onset. Hopefully as the nitronate was formed the imine, being present in excess, would immediately intercept it to provide the desired product. This reaction was also monitored *via* ^1H NMR, but again no product-like peaks were observed. In this case the reaction was much less well defined, and it appears that β -nitronitrile **202-a** isn't formed under these conditions (**Scheme 81**).



Scheme 81: Unsuccessful tandem 1,4-addition/nitro-Mannich conditions

Finally, a deprotonation study was undertaken. We thought a more traditional stepwise reaction (*i.e.* 1,4 addition and isolation of the β -nitronitrile followed by deprotonation and addition of imine and acid to undergo a nitro-Mannich reaction) would allow us to investigate the effect an α - nitrile stereocentre has upon the diastereoselectivity of a nitro-Mannich reaction. The β -nitronitrile **202-a** was dissolved in THF, cooled to -78°C and 1.1 eq. of $n\text{BuLi}$ added. The reaction was then warmed to rt for 30 min, and quenched with the addition of deuterated acetic acid. Although there was 88 % D incorporation, there was only a 50 % mass recovery. As nitro-alkene **197** resulting from elimination of HCN from **202-a** is highly volatile, it is quite probable that the remainder of the mass is due to this elimination and subsequent loss of the alkene through work-up (**Scheme 82**). Due to this series of poor results, and some much more promising results along a different line of enquiry, work on this project was ceased.



Scheme 82: Deprotonation of β -nitronitrile **202-a**

2.2.4 Potassium Ferrocyanide

Having fully optimised the 1,4-addition of cyanide to a nitro-alkene using acetone cyanohydrin, one last effort to achieve the desired 1,4-addition/nitro-Mannich reaction was attempted. Recently a large amount of research has focused on using potassium ferrocyanide as a nitrile source in palladium couplings.¹⁰³ The key advantage is the low toxicity associated with the reagent. The toxicity is so low that the reagent is used in the food industry for metal precipitation and as an anti-agglutinating agent.¹⁰⁴ The other major advantage is that all six of the cyanides are available for transfer under the palladium-catalysed protocols, making it cheaper per cyanide than potassium cyanide. Although there is no literature precedent for this source of cyanide adding to conjugated systems, we decided to investigate if it would be possible to use potassium ferrocyanide as a cyanide anion surrogate. Initially, taking 10 mol % Pd(OAc)₂, 20 mol % dppf, 0.4 eq K₄[Fe(CN)₆], 1.2 eq Na₂CO₃ and 1.0 eq of β -nitrostyrene **213** in DMF and heating at 120 °C for 16 h in a sealed tube^{103a} we isolated, after chromatography, a bright yellow solid. As none of the analytical data fitted with any expected products (for example the elemental analysis indicated no nitrogen present!), attempts at crystal growth were undertaken. The X-ray diffraction revealed the product to be 1,3,5-triphenylbenzene **214** (**Figure 17**).

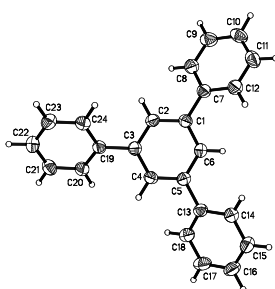
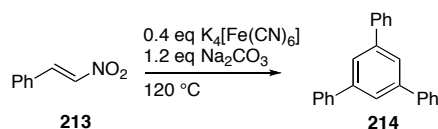


Figure 17: X-ray structure of unknown compound, shown to be 1,3,5-triphenylbenzene **214**

Further experimentation indicated that the presence of palladium was not necessary, and indeed the reaction was cleaner and higher yielding in its absence (**Table 9**). In the absence of base no reaction was observed, and the starting β -nitrostyrene **213** degraded, presumably due to the prolonged heating. The reaction was also amenable to microwave heating, with the reaction at 85 % conversion after 60 min at 120 °C. If the reaction was carried out in DMSO under conventional heating a much lower yield was observed, and only 50 % conversion was seen under microwave heating after 60 min at 120 °C.

Table 9: Optimisation for formation of **214**



Entry	Solvent	Heating	Time	Conversion / %	Yield / %
1 ^a	DMF	Conventional	16 h	100	61
2 ^b	DMF	Conventional	16 h	0	0
3	DMF	Conventional	16 h	100	84
4	DMSO	Conventional	16 h	100	17
5	DMF	Microwave	10 min.	60	43
6	DMF	Microwave	60 min.	85	70
7	DMSO	Microwave	10 min.	30	n.d.
8	DMSO	Microwave	60 min.	50	n.d.
9 ^c	DMF	Conventional	16 h	0	0

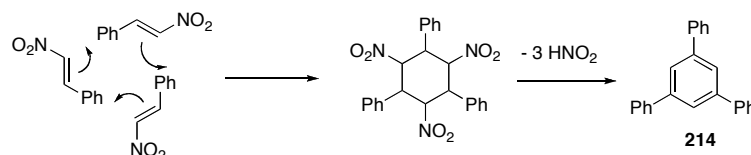
^a 10 mol % Pd(OAc)₂ and 20 mol % dppf added before heating.

^b No base added to reaction.

^c No K₄[Fe(CN)₆] added to reaction

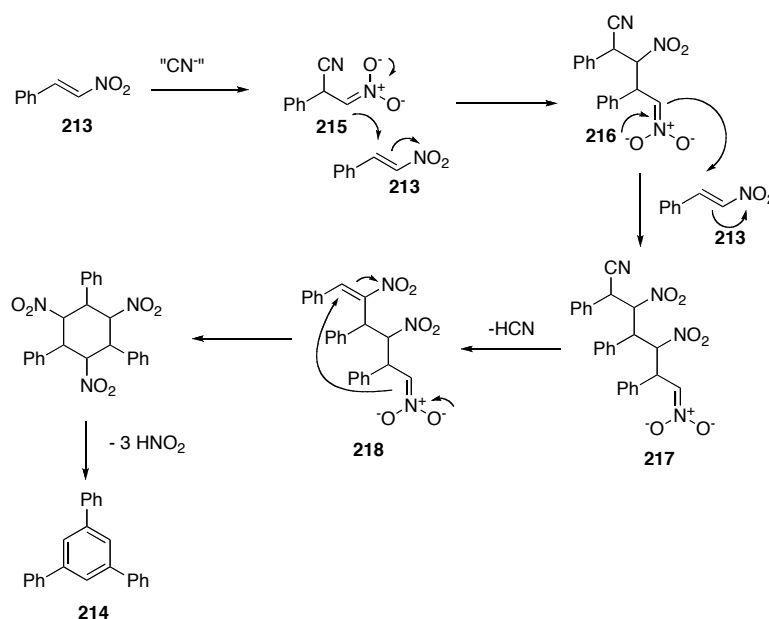
The mechanism for the formation of **214** could be explained by two possible pathways. The first is a [2+2+2] cycloaddition of nitro styrene, followed by aromatisation by elimination of HNO₂ as shown in **Scheme 83**. We believe this

mechanism can be discounted as there is no involvement of the $K_4[Fe(CN)_6]$, and in the absence of $K_4[Fe(CN)_6]$ no reaction takes place (entry 9). A more realistic mechanism, proposed by Zard *et al.*¹⁰⁵ for a similar system, is shown in **Scheme 84**.



Scheme 83: Discounted [2+2+2] cycloaddition aromatisation mechanism

The mechanism involves initial 1,4-addition of cyanide to a molecule of β -nitrostyrene **213**. The nitronate **215** thus generated then adds to another molecule of **213** generating a new nitronate **216**. Once again addition to another molecule of **213** provides another nitronate **217**. Elimination of HCN and cyclisation onto the resultant nitro-alkene **219** followed by subsequent elimination of three molecules of HNO_2 provides **214**. Obviously there are a number of alternate pathways and side reactions that could lead to the same product, for instance the point at which the HCN eliminates could be at any point after the formation of **216**, however, these have been omitted for reasons of clarity.



Scheme 84: Alternate mechanism for formation of **214**¹⁰⁵

Although the reaction product is not the desired one, the reaction appears to proceed through the desired intermediate **215**. The initial reaction conditions were quite concentrated (1 M), which would increase the likelihood of **215** encountering another molecule of **213**. When the reaction concentration of **213** was diluted by a factor of ten the result was only a lowering of the yield to 51 %. Potentially with further optimisation it may be possible to achieve the desired 1,4-addition (perhaps by using a slow addition of nitro styrene to the reaction mixture), however, we decided to pursue another more productive avenue of research, details of which can be found in the following section.

2.3 Dialkylzinc Addition

In order to achieve the desired 1,4-addition/nitro-Mannich reaction, attention shifted from cyanide to diethylzinc. This reagent was chosen for a number of reasons. Firstly there is much literature precedent for the copper catalysed addition of this reagent to nitro-alkenes, and also a variety of asymmetric protocols (see section 1.3). Nitro-alkene **213** was chosen as the substrate for the initial reactions, and when combined with diethylzinc a model system with three differently sized groups was conceived. As the 1,4-addition centre (**Figure 18**, label a) is a stereocentre, there is the possibility of relative stereocontrol to be passed on to the subsequently created nitro-Mannich stereocentres (**Figure 18**, labels b and c). With the model system we hoped to maximise the potential of chirality transfer by creating a stereocentre that could maximise facial discrimination of the intermediate nitronate anion **219**. This was achieved by having two substituents, in addition to hydrogen, that were as sterically different as possible. The ethyl group (A -value = 1.79 kcal/mol)¹⁰⁶ is very different from the phenyl group (A -value = 2.80 kcal/mol).¹⁰⁶ This hypothesis, however, suggests that alkyl additions to alkyl nitro alkenes or aromatic additions to nitro styrenes would not show good relative stereocontrol across all three stereocentres, due to poor facial discrimination. In view of the excellent levels of stereocontrol achieved in the previous hydride triggered reaction (**Scheme 71**), we were confident that stereocontrol across the b-c bond would be achieved, most likely in the form of an *anti*-relationship. The relationship between the a-b bond, however, was an unknown situation, as there is little literature precedent for nitro-Mannich reactions where the nitro-partner contains an α -stereocentre (see section 1.4).

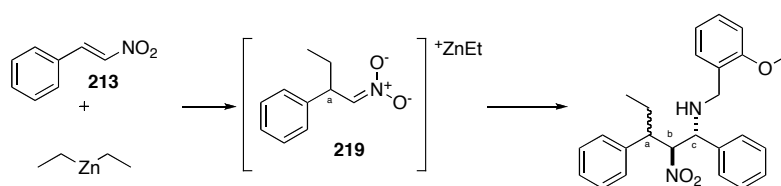


Figure 18: The model system

Initially, due to the success provided with OMB protected imine **212** in the reductive nitro-Mannich protocol,⁹³ this material was used. Simply taking β -nitrostyrene **213**, 5 mol % copper (II) triflate and 1.1 eq of diethylzinc in THF the 1,4 addition was complete in 90 min (observed by TLC). At this stage the solution was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of imine **212** (2.0 eq) in THF was added, followed by a 1:1 mixture of TFA: THF (3.5 eq). After 1 h at $-78\text{ }^{\circ}\text{C}$ the reaction was warmed to rt and stirred for a further 1 h. After work up a crude ^1H NMR showed a 1:1 ratio of diastereomers (only two of the possible four were observed), however, the material was taken on in its crude state in order to protect the amine as its trifluoroacetamide. This protection has been shown to be necessary due to the instability of the β -nitro-amines.^{93, 19} After purification only a single diastereoisomer was isolated in 34 % yield, and later x-ray crystallography showed it to be the *syn/anti*-isomer **220** (**Figure 19**). Presumably the second isomer was unstable or unreactive to the trifluoroacetate-protection conditions (*vide infra*). Whilst a disappointing result in terms of yield, it seemed that at least a small amount of diastereo-control was occurring, as only two out of four possible diastereoisomers were observed. This selectivity, however, can most likely be attributed to the strong *anti*-preference of the β -nitroamine unit.

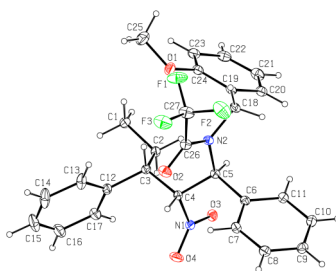
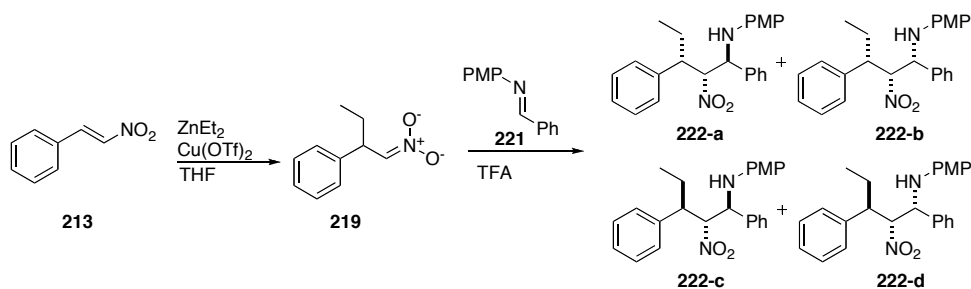


Figure 19: X-ray structure of isomer **220**

In order to improve this diastereoselectivity an alternative imine protecting group was trialled. The *para*-methoxy phenyl (PMP) group has been used previously within the group with good results, and was the obvious choice. An exact repeat of the previous conditions but with imine **221** rather than imine **212** provided a 4:1:1:0 ratio of diastereoisomers. Later x-ray crystallography showed that the major diastereoisomers were **222-a** and **222-b**. The third diastereoisomer has so far remained elusive in terms of a crystal structure, but is presumed to be **222-c**, *vide infra*. At this stage the project was continued as a collaboration with another doctoral student, Dr G. Stepney.



Scheme 85: Repeated conditions using imine **221**

With the promising initial result a solvent screen was initiated (**Table 10**). In all of the following tables the ratios quoted were determined by ^1H NMR spectroscopy, and are rounded to the nearest 5. In all cases the

diastereoselectivity was determined by comparison of the $CHNO_2$ signals (~ 5 ppm) or the $CHEt$ signals (~ 3.5 ppm). As will be seen the fourth diastereoisomer **222-d** is always attributed a value of 0. Due to the crude nature of the spectra, it is impossible to rule out completely that this diastereoisomer is formed, however, we have not isolated a single example of this diastereoisomer, and believe that if any is formed, it is to an extent of less than 5 %, and can easily be ignored.

Table 10: Solvent screen^a

Entry	Solvent	Conversion to 219 ^c	Ratio 222 - (a : b : c : d) ^c
1 ^b	TBME	> 95 %	20:75:5:0
2 ^b	Et ₂ O	> 95 %	10:85:5:0
3 ^b	<i>t</i> Pr ₂ O	> 95 %	10:85:5:0
4	DCM	> 95 %	10:80:10:0
5 ^b	PhMe	85 %	25:70:5:0
6	DME	80 %	45:10:45:0
7	THF	> 95 %	75:20:5:0
8	EtOAc	> 95 %	60:25:15:0
9	DMF	< 10 %	-
10	THF (10 % HMPA)	50 %	50:50:0:0
11	EtCN	< 10 %	-
12	1,4-Dioxane	25 %	-

^a Reactions carried out with 5 mol % Cu(OTf)₂, 1.1 eq ZnEt₂, 2 eq imine, 3.5 eq TFA, stirred at -78 °C for 1 h, then at rt for a further 1 h.

^b Result provided by G. Stepney.

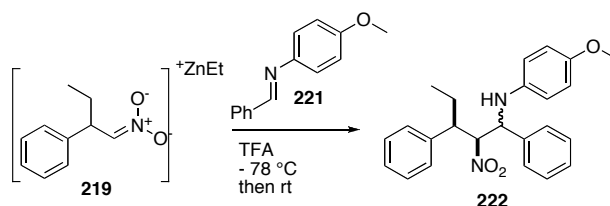
^c As determined by ¹H NMR.

As can be seen from **Table 10** there is a remarkable solvent dependency on the stereochemical outcome of the reaction. Reactions in more Lewis basic solvents (entries 6-8) provided *syn/anti*-isomer **222-a** as the major product, whilst those performed in less Lewis basic solvents (entries 1-5) provided *syn/syn*-isomer **222-b** preferentially. The reason for this selectivity will be discussed in more detail later, however, the salient observation noted was that in the reactions where the *syn/syn*-isomer **222-b** was preferentially formed the reactions were heterogeneous, and conversely the reactions where *syn/anti*-isomer **222-a** predominated were homogeneous. Those entries where the conversion of the 1,4 addition was low were disregarded immediately. In order to gain access to two diastereoisomers it was decided to optimise the reaction conditions separately in THF and Et₂O. Dr G. Stepney carried out the optimisation of the reaction in Et₂O,¹⁰⁷ whilst the optimisation of the reaction in THF will be discussed in the following pages.

Having shown that THF was the solvent of choice for preferential formation of *syn/anti*-isomer **222-a**, reaction conditions were examined in order to further optimise the process. The first variable looked at was reaction time. In the initial result (**Table 10**, entry 7) after nitronate formation the reaction was cooled to - 78 °C, imine and TFA were then added, and the reaction allowed to stir at - 78 °C for 1 hour, then removed from the cold bath and stirred at ambient temperature for a further hour. Clearly there are 3 points of variability in the reaction times; the length held at - 78 °C, the time left at ambient temperature and the time taken to warm the reaction to ambient temperature. As can be seen from **Table 11** a small period of time at - 78 °C is essential for diastereoselectivity, however, the length of this time seems to be immaterial over 60 min (entries 1, 2 and 4). The length of time the reaction is held at ambient temperature, however, plays a much greater role. If the reaction is quenched after just an hour at - 78 °C there is little selectivity, and low conversion. After 5

min at rt the diastereoselectivity is at the highest, in favour of the *syn/anti*-isomer **222-a** (entry 2), with a slow drop off over time towards the *syn/syn* isomer **222-b** (entries 3, 5 and 6). At 24 hours the ^1H NMR begins to become less clear, perhaps an indication of product degradation, and the ratio **222-a:222-b:222-c** is hard to clearly define due to additional peaks obscuring those of the products.

Table 11: Optimisation of reaction time^a



Entry	Time at - 78 °C min	Time at ambient min	Conversion to nitro-amine ^b %	Ratio 222- (a:b:c:d) ^b
1	5	5	90	50:50:0:0
2	60	5	> 95	85:10:5:0
3	60	60	> 95	60:20:20:0
4	240	5	91	85:10:5:0
5	240	30	> 95	70:20:10:0
6	60	960	87	45:45:10:0
7	60	5 ^c	> 95	50:40:10:0
8	60	5 ^d	> 95	75:15:10:0

^a Reactions carried out with 5 mol % Cu(OTf)₂, 1.1 eq ZnEt₂, 2 eq imine, 3.5 eq TFA in THF.

^b As determined by ^1H NMR.

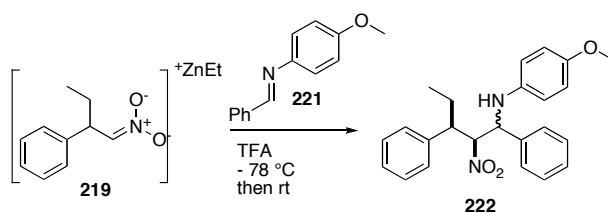
^c Reaction vessel placed in a water bath at rt.

^d Reaction placed in an acetonitrile/dry ice bath (- 42 °C).

The next parameter under examination was equivalents of imine (**Table 12**). In all cases the number of equivalents of TFA was set as the number of equivalents imine plus 150 % extra, as this has been shown to give the best results in

previous protocols.⁹³ If a single equivalent of the imine was used the diastereoselectivity was slightly reduced, however, more importantly the conversion to nitro-amine (measured by consumption of nitronate **219**) was much lower (entry 2). Using a larger excess of the imine (3.0 eq) barely affected the diastereoselectivity (entry 6), so shows no improvement over using 2.0 equivalents, whilst at 1.2 and 1.5 eq the diastereoselectivity is affected, as is the conversion to nitro-amine (entries 3 & 4). Whilst the diastereoselectivity and conversion observed using only 0.5 eq of imine (entry 1) is comparable to that observed when using 2.0 eq, it was thought the nitroalkene was considered the more valuable partner, and using an excess of the imine was more desirable.

Table 12: Optimisation of imine stoichiometry^a



Entry	imine eq	Conversion to nitro-amine ^b	Ratio 222 - (a:b:c:d) ^b
1	0.5	>95	90:5:5:0
2	1.0	83	75:15:10:0
3	1.2	92	70:15:15:0
4	1.5	>95	75:15:10:0
5	2.0	>95	85:10:5:0
6	3.0	>95	85:10:5:0

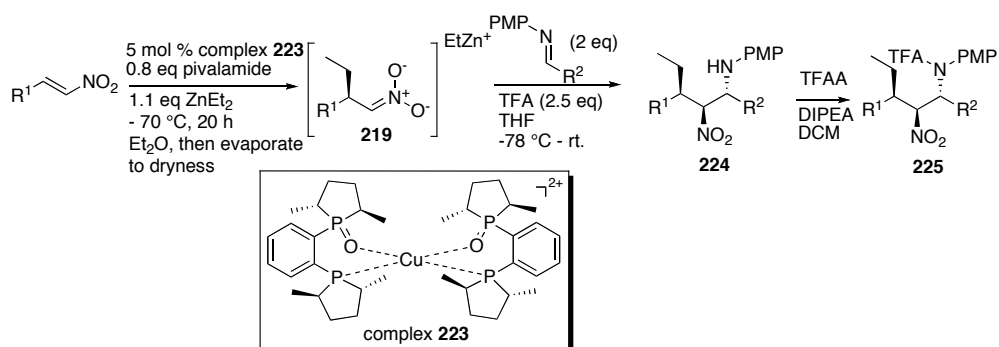
^a Reactions carried out with 5 mol % Cu(OTf)₂, number of eq of imine plus 1.5 eq TFA in THF, stirring for 1 h at -78 °C followed by 5 min. at rt

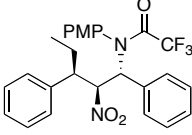
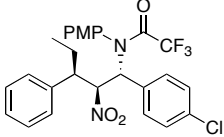
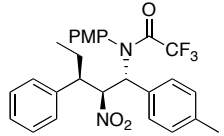
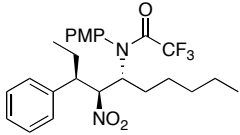
^b As determined by ¹H NMR.

Having fully optimised the reaction, effort was now focused on isolation of the products. As before the crude material after aqueous work-up was treated with trifluoroacetic anhydride (TFAA) and DIPEA to afford the trifluoroacetamide. At this stage only two diastereoisomers were isolated as the trifluoroacetamides, and it was later discovered that the *syn/syn*- isomer is inert to the protection, even under forcing conditions.⁹³ The conditions attempted, in addition to the standard procedure, included the use of pyridine or DMAP as the base, extended reaction times, heating (refluxing DCM) and the use of trifluoroacetyl chloride. The ratio of the two isomers isolated was 90:10 after chromatography. This ratio shows a slight increase in favour of the major isomer compared to the crude reaction mixture. This enrichment is due to slight separation of the two diastereoisomers by chromatography. Having fully optimised the reaction conditions the scope of the reaction was explored. A series of imines and β -nitrostyrenes were examined under the reaction conditions (**Tables 13-16**).

In order to demonstrate just how adaptable the reaction is to various conditions we chose a selection of electron neutral, rich and poor aromatic, heteroaromatic (furyl and thiophenyl), alkyl and functionalised (α -imino-ester) imines, and reacted them with a similar range of nitro-alkenes, as well as using two different ligand systems and three organozinc reagents (Et, Me and Ph). The two ligands were chosen for their (relatively) low cost and ease of preparation, as well as their wide scope and consistently high *ee*'s. The first ligand used was the *bis*-phosphine-mono-oxide ligand **223** used by Charette *et al.*⁶² Charette reports two different methods for the use of this ligand. Either the ligand and copper (II) triflate are added with the other reagents at the start of the reaction, or the ligand can be pre-complexed to the copper. In our hands the second method proved to be more reliable, as the copper/ligand stoichiometry is fixed at the correct amount, whilst adding the reagents and copper separately can easily result in a slight imbalance in the ratio, especially when weighing out small quantities of

catalyst (< 5 mg). These conditions are particularly sensitive to ligand copper stoichiometry, and indeed an excess of the ligand (or a dummy ligand, pivalamide) is required in order to promote a monomeric copper species. Charette reports that the monomer is far more effective than the dimer in terms of asymmetric induction. Solvent also plays a key role in the asymmetric outcome of the addition, as well as in the diastereoselectivity observed within our nitro-Mannich reaction. The only solvent that provides high levels of asymmetry for the Charette protocol is Et₂O. Tetrahydrofuran is required to access the desired *syn/anti*- β -nitroamines, but the initial 1,4-addition was carried out in Et₂O as described by Charette. After the 1,4-addition reaction was judged complete by TLC analysis (approximately 16-20 h) the imine and TFA were added at – 78 °C in the required amount of THF. Unfortunately the presence of Et₂O was detrimental to the diastereoselectivity of the reaction, with only a slight favouring of *syn/anti*-**222-a** over *syn/syn*-**222-b**. In order to overcome this solvent issue the 1,4-addition was carried out in Et₂O as before, and was then removed under high vacuum at rt prior to the addition of THF (2 mL), then the imine and TFA in THF at -78 °C. In this way the results obtained in **Table 13** were achieved.

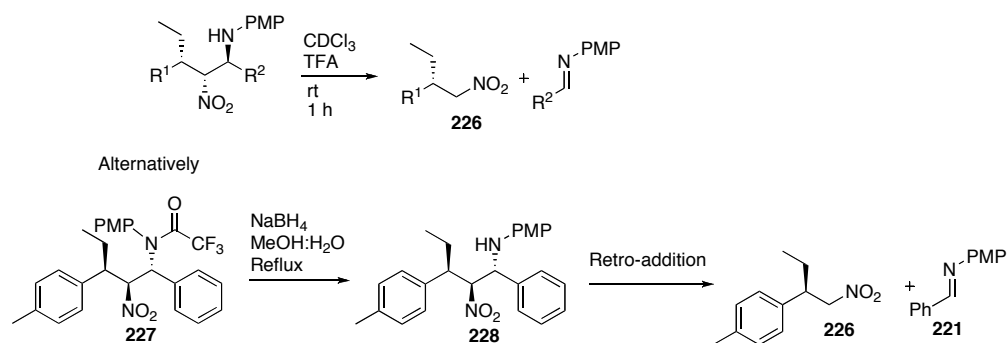
Table 13: Reaction scope using Charette protocol

Entry	Product	Analogue	Ratio 224 - (a:b:c:d) ^a Crude	Ratio 225 - (a:b:c:d) ^a Final	Yield ^b %	ee ^c %
1	225-1		85:10:5:0	90:0:10:0	73	86
2	225-2		55:15:30:0	80:0:20:0	59	85 ^d
3	225-3		75:15:10:0	95:0:5:0	61	85 ^d
4	225-4		95:5:0:0	100:0:0:0	68	90 ^d

^a As determined by ¹H NMR. a = *syn/anti*, b = *syn/syn*, c = *anti/anti*, d = *anti/syn*.^b Isolated yield.^c Measured by chiral HPLC (OD-H column, 99.5 % hexane 0.5 % IPA).^d Measured by chiral HPLC of parent nitro-alkane (OD-H column, 98 % hexane, 2 % IPA).

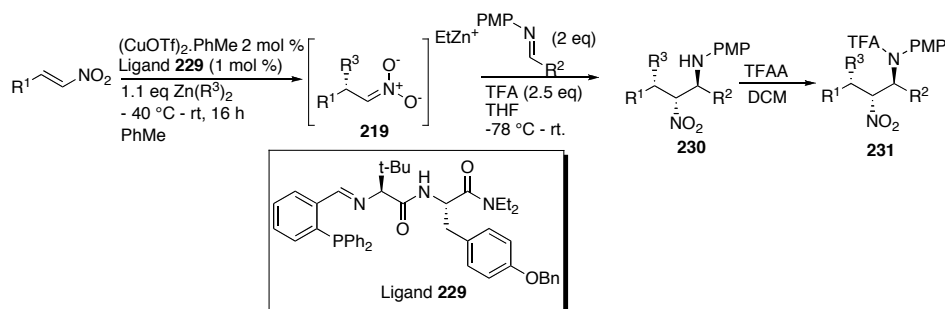
The crude ratio refers to the ratio of diastereoisomers after work-up of the nitro-Mannich step. The final ratio refers to the ratio obtained after protection as the trifluoroacetamide and chromatography, and was again determined by ^1H NMR as for the crude material. In all cases trifluoroacetamide formation results in an enrichment in favour of the major *syn/anti*-diastereoisomer. As has been mentioned previously the *syn/syn* isomer is inert to the trifluoroacetate protection, and degrades to the imine and 1,4-addition product under the protection conditions. The remaining enrichment presumably comes from separation of the minor diastereoisomers by chromatography.

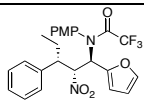
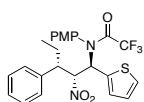
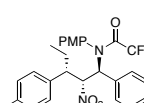
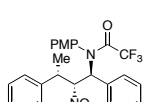
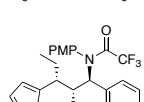
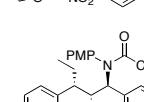
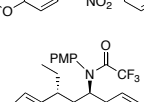
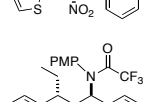
During the course of the determination of the *ee* of the products by chiral HPLC, a number of the analogues could not be resolved. For the determination of the *ee* of these products degradation was necessary. The easiest method of degradation was through a retro-nitro-Mannich reaction. In the case of entries 2, 3 & 4, **Table 13**, and entry 7, **Table 14**, the NMR sample used to determine the crude diastereomeric ratio was used. The *syn/anti*- β -nitroamines were unstable in CDCl_3 solution over a period of approximately 48 hours, and after this time had undergone complete retro-addition, as observed by ^1H NMR analysis. Alternatively the addition of a single drop of trifluoroacetic acid increases the speed of the reaction, and the retro-addition is complete in less than an hour. The sample can then be passed through a short pipette column using a low polarity mobile phase to give the parent nitro-alkane **226**. The second method used to measure the *ee* of entry 3, **Table 14**, took the trifluoroacetamide-protected species **227** and removed the trifluoroacetyl group using NaBH_4 . The reaction was followed by TLC and showed complete deprotection. After an acidic work-up the PMP-protected β -nitroamine **228** underwent spontaneous retro-addition, again allowing the parent nitro-alkane **226** to be isolated and assayed by HPLC.



Scheme 86: Use of NMR sample and trifluoroacetamide deprotection to obtain nitro-alkanes

As the *ee* of the final product is determined by the *ee* of the initial 1,4-addition, it follows that the *ee* of the nitro-alkane **226** obtained from retro-addition is identical to the *ee* of the β -nitroamine product. Measuring the *ee* of a resolvable example, and comparing this to the *ee* of the degraded sample showed this was the case.⁹³

Table 14: Reaction scope using Hoveyda protocol

Entry	Product	Analogue	Ratio ^a 230- (a:b:c:d) Crude	Ratio ^a 231- (a:b:c:d) Final	Yield ^b %	ee ^c %
1	231-1		90:10:0:0	100:0:0:0	69	85
2	231-2		95:5:0:0	100:0:0:0	74	95
3	231-3		70:15:15:0	85:0:15:0	70	90 ^d
4	231-4		85:10:5:0	100:0:0:0	62	98
5	231-5		90:10:0:0	100:0:0:0	74	89
6	231-6		90:10:0:0	100:0:0:0	73	90
7	231-7		80:10:10:0	90:0:10:0	80	90 ^d
8 ^e	225-1		85:10:5:0	90:0:10:0	64	-

^a As determined by ¹H NMR. a = *syn/anti*, b = *syn/syn*, c = *anti/anti*, d = *anti/syn*.^b Isolated yield.^c Measured by chiral HPLC (OD-H column, 99.5 % hexane 0.5 % IPA).^d Measured by chiral HPLC of parent nitro-alkane (OD-H column, 98 % hexane, 2 % IPA).^e Synthesised by the addition of Ph₂Zn to 1-nitrobut-1-ene.

The second ligand system used was that described by Hoveyda *et al.* (**Table 14**)⁶¹ Again there were issues over the solvent of choice. The procedure described by Hoveyda uses toluene. The initial 1,4 addition was carried out in toluene, and when complete the imine and TFA were added at -78 °C in the required amount of THF. Again the diastereoselectivity was affected by the presence of toluene. The 1,4-addition of diethylzinc to β -nitro styrene was carried out as described by Hoveyda, but using THF as the solvent. This resulted in the isolation of the product in comparable yield, but much lower *ee* (approximately 50 %, measured by HPLC analysis). This problem was once more overcome with the aid of a solvent swap into THF after the 1,4-addition was judged complete. Removal of the toluene under high vacuum at 30 °C followed by the addition of THF (2 mL) then the addition of the imine and TFA in THF at - 78 °C allowed for the results in **Table 14**. We also chose to investigate the addition of different diorganozinc reagents to nitro-alkenes in order to further test the scope of the reaction. Pleasingly dimethylzinc (entry 4) provided the desired β -nitroamine in good yield and excellent *ee*. We also investigated the addition of diphenylzinc to 1-nitrobut-1-ene. Diphenylzinc is supplied as a white solid, and must be handled in a glove box. Unfortunately diphenylzinc did not give any enantioinduction with the Hoveyda ligand, and no conversion with the Charette ligand. There is no literature precedent for the use of diphenylzinc in asymmetric addition to a nitro-alkene, however, there is some precedent for the addition of diphenylzinc to enones,¹⁰⁸ and with some experimentation one of these systems could possibly be adapted to the desired substrates. In this respect, of particular interest is the methodology developed by Hoveyda *et al.*^{108b} that uses a similar, but far simpler amino acid based ligand **232** (**Figure 20**). Due to time constraints this was not investigated in this study.

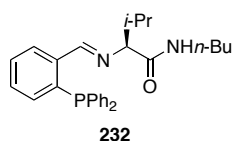
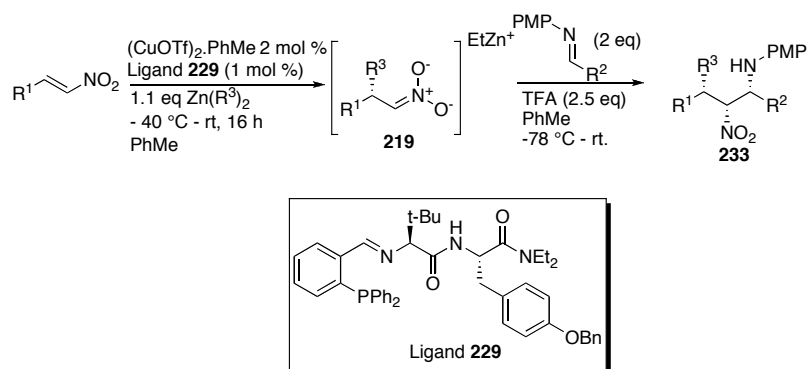


Figure 20: Structure of ligand **232**

For each of the entries in **Tables 13** and **14** G. Stepney obtained an equivalent result for the *syn/syn*-diastereoisomer.⁹³ However, some of the analogues were chosen after the completion of G. Stepney's studies. The results shown in **Table 15** were obtained by following the procedures optimised by G. Stepney, with some minor adjustments. The standard conditions entailed addition of diethylzinc (1.1 eq) to β -nitro styrene (1.0 eq) in toluene. After the 1,4-addition was judged complete (TLC analysis) the reaction was cooled to -78 °C and a solution of imine (2.0 eq) in toluene was added, followed by a 1:1 mixture of TFA (3.5 eq) in toluene. The reaction was stirred at -78 °C for 2 h, then at rt for a further 1 h. In the case of entry 3 (R^1 = Ph, R^2 = 2-thiophenyl, R^3 = Et), following the standard conditions the product could not be obtained pure. Whilst the ratio of diastereomers of the crude reaction and the final product, as well as the yield based on ^1H NMR were in line with the other analogues, the separation of the product from residual imine (2.0 eq are required for high conversion and good diastereoselectivity) by column chromatography was minimal. Using the imine as the limiting reagent, and having 2.0 eq of the nitro-alkene overcame this problem. The excess nitroalkane generated was easily separated from the desired product, and provided the pure product in good yield and *ee*. The conditions employed for entry 5 (R^1 = *p*-NO₂-C₆H₄, R^2 = 2-Ph, R^3 = Et) were also slightly modified. The solubility of *para*-nitro- β -nitrostyrene in Et₂O and toluene is minimal. In fact the only solvent found to dissolve the starting material to any extent was THF. Unfortunately this precluded the use of either of the asymmetric protocols, as even after prolonged stirring under the reaction

conditions little (< 20 %, Hoveyda protocol) or no (Charette protocol) reaction was observed. By using THF as the solvent for the 1,4-addition, then replacing with Et₂O for the nitro-Mannich step the product was isolated in acceptable yield, with excellent diastereoselectivity in racemic form.

Table 15: *Syn/syn*-diastereoisomer analogues



Entry	Product	Analogue	Ratio ^a 233 - (a:b:c:d) Crude	Ratio ^a 233 - (a:b:c:d) Final	Yield ^b %	ee ^c %
1	233-1		5:95:0:0	0:100:0:0	77	93
2	233-2		5:95:0:0	0:100:0:0	77	86
3 ^d	233-3		5:95:0:0	0:100:0:0	75	95
4 ^e	233-4		15:85:0:0	0:100:0:0	63	-
5 ^f	233-5		10:90:0:0	0:100:0:0	54	-

^a As measured by ¹H NMR. a = *syn/anti*, b = *syn/syn*, c = *anti/anti*, d = *anti/syn*.

^b Isolated yield.

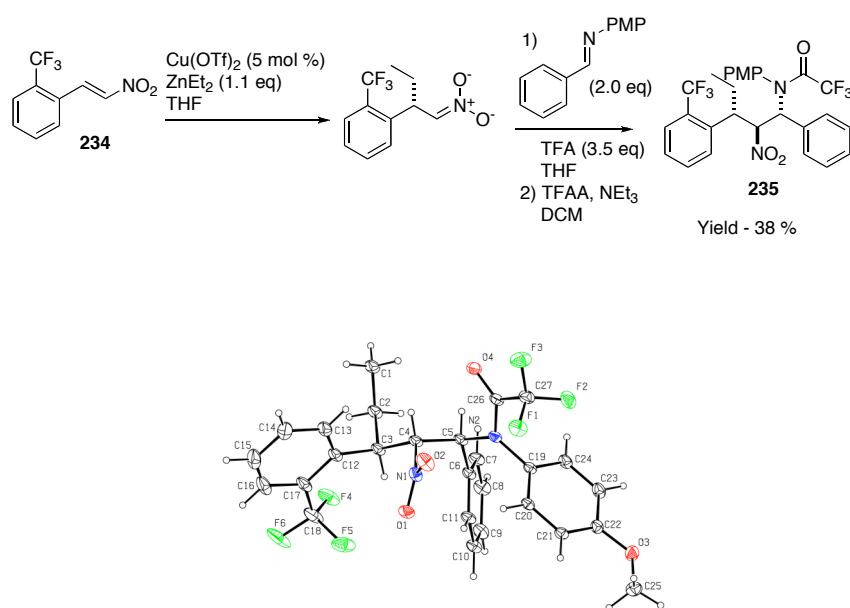
^c As measured by HPLC (OD-H column, 99.5 % hexane, 0.5 % IPA).

^d Reaction performed using imine as limiting reagent.

^e Synthesised by the addition of Ph₂Zn to 1-nitrobut-1-ene.

^f 1,4-Addition carried out in THF, solvent swapped prior to addition of imine.

During the course of analogue synthesis the large majority of the products followed the pattern observed for the initial trial substrate, *i.e.* if the reaction was carried out using THF the *syn/anti*-diastereoisomer was observed (backed up by several crystal structures), whilst if the solvent used was Et₂O the *syn/syn*-isomer was isolated. There are, however, some exceptions. The use of *ortho*-trifluoromethyl- β -nitro styrene **234** led to the isolation of the *anti/anti*-diastereoisomer **235** (Scheme 87), previously the minor isomer with other substrates.



Scheme 87: Reaction scheme and crystal structure of the trifluoroacetamide of **235**

Table 16 lists the reactions undertaken with the aim of understanding the origins of the unusual diastereoselectivity. As can be seen from entry 1, the crude ratio is in line, in terms of magnitude, with the other examples, but differs in that it is the *anti/anti* stereochemistry that predominates. The yield is much lower than the other examples, and this can be put down to lower stability of the β -nitroamine (complete retro-addition of a CDCl₃ sample was observed after 60

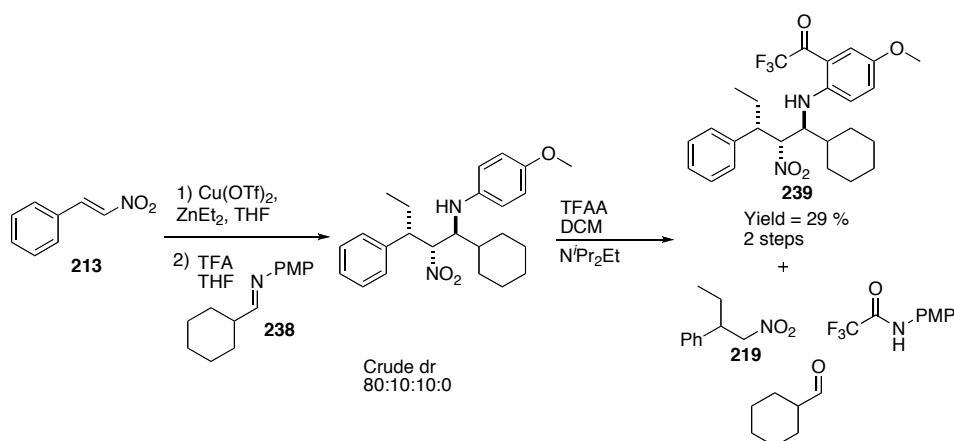
min compared with ~48 h for *syn/anti*-diastereoisomer). In order to investigate whether the unusual diastereoselectivity was due to sterics or electronics around the nitro-styrene, or both, a number of substrates were chosen to probe this. A *para*-electron-withdrawing group (entry 2) gave a much lower yield than would be expected, but provided the expected sense and magnitude of the *syn/anti*-diastereoisomer. If the equivalent reaction was carried out in Et₂O a slightly lower than usual yield was observed, but the sense and magnitude of the diastereoselectivity was as expected (*i.e.* *syn/syn*). Unfortunately *para*-trifluoromethyl- β -nitrostyrene (entries 9 and 10) gave no observable reaction. Whether this is due to the destabilising influence of the trifluoromethyl group on the β -nitroamine product (the unprotected form of β -nitroacetamide **235** is less stable than expected), or an electron-withdrawing group in the ring affecting the reactivity of the intermediate nitronate is impossible to tell, entries 1 and 2 both being low yielding. Substituting an *ortho*-methoxy group into the aromatic ring provides a 1:1 mixture of diastereoisomers, separable by chromatography, but again in very low yield (5 % in total). Unfortunately it proved impossible to corroborate the sense of diastereoselectivity with a crystal structure, neither of the diastereoisomers providing crystals of sufficient quality to permit x-ray crystallography. The assignment of the stereochemistry was based on the observation that the *syn/syn*-diastereoisomer undergoes degradation during TFA protection, and the *anti/syn*-diastereoisomer has never been observed. An *ortho*-methyl group again provided no result, either due to no reaction or degradation of the products during work up. Unfortunately this series of inconclusive results does not allow any convincing arguments regarding the reason for this unusual diastereoselectivity to be reached.

Table 16: Control reactions

Entry	Product	Analogue	Solvent	Ratio ^a 236- (a:b:c:d) Crude	Ratio ^a 237- (a:b:c:d) Final	Yield ^b %
1	235		THF	5:10:85:0	5:0:95:0	38
2	237-2		THF	75:5:20:0	90:0:10:0	38
3	233-5		Et ₂ O	10:90:0:0	0:100:0:0	54
4	237-3		THF	50:0:50:0	50:0:50:0	5
5	237-4		Et ₂ O	na	na	0
6	237-5		Et ₂ O	na	na	0
7	237-6		THF	na	na	0
8	237-7		Et ₂ O	na	na	0
9	237-8		THF	na	na	0
10	237-9		Et ₂ O	na	na	0

^a As measured by ¹H NMR. a = *syn/anti*, b = *syn/syn*, c = *anti/anti*, d = *anti/syn*.^b Isolated yield.

One other example also provided an anomalous result, however, the anomaly was not related to the relative stereochemistry of the product, rather the actual product (**Scheme 88**). As expected the 1,4-addition of diethylzinc to β -nitrostyrene **213** followed by the addition of cyclohexyl imine **238** proceeded with reasonably good diastereoselectivity (80:10:10:0). The crude material was then subjected to the standard trifluoroacetamide protection conditions (trifluoroacetic anhydride, Hünig's base in DCM), but the amide was not isolated. Instead a small amount of **239** (29 %, 2 steps) was isolated as the only nitro-Mannich product, along with the excess imine degradation products, and nitro-alkane **219**. There are two possible mechanisms for the formation of **239**, either a Friedel-Crafts acylation, or a Fries-rearrangement. Although Friedel-Crafts acylations using protic acids are known, the conditions required are very harsh, usually requiring refluxing and a superstoichiometric amount of a strong acid. This leads us to believe **239** was formed firstly through acylation on nitrogen, then subsequent rearrangement. This is, in itself, quite a rare reaction. The large majority of aniline based Fries-rearrangements are photochemical reactions,¹⁰⁹ and only a limited amount of literature is available on this type of thermal process, however temperatures in excess of 120 °C are reported.¹¹⁰

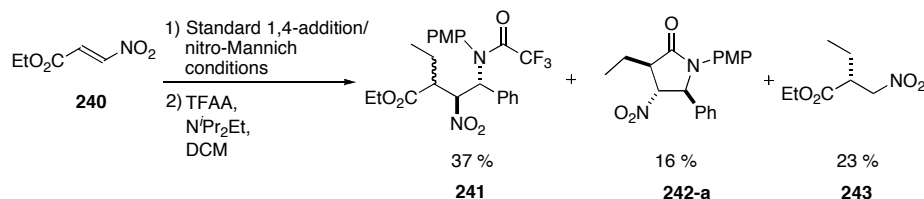


Scheme 88: 1,4-Addition/nitro-Mannich reaction followed by acylation on carbon

The reason in this case why acylation, be it through a Fries rearrangement or a Friedel-Crafts acylation, occurs on carbon rather than nitrogen is unknown. Arguments based on some electronic effect imparted by having a non-aromatic group on the imine can be discounted on the basis that the *n*-hexanal-derived imine behaves as expected (**Table 13**, entry 4). The second possibility is a steric factor. If the cyclohexyl group has a significantly different size to a phenyl group, it is possible that this may cause a conformational change that may favour acylation on carbon rather than nitrogen. Based on *A*-values a cyclohexyl group is smaller than a phenyl group (2.15 vs 2.80 kcal/mol). As a *n*-pentyl chain (*A*-value for ethyl = 1.75 kcal/mol) is smaller than a cyclohexyl group (2.15 kcal/mol)¹⁰⁶ based on the same parameter, this argument can too be discounted, as the anomaly lies intermediate in size between two groups that behave as expected. It is clear that the result must be due to a subtle mixture of sterics and electronics, and thus cannot easily be rationalised.

One final curiosity observed during examination of the scope of this reaction occurred when nitro-alkene **240** was examined (**Scheme 89**). The 1,4-addition/nitro-Mannich reaction proceeded as expected. If the standard conditions (THF, 1 h at – 78 °C followed by 5 min at rt) were followed, after the trifluoroacetamide protection a mixture of the expected, acyclic β -nitrotrifluoroacetamide **241** and pyrrolidone **242-a** was isolated, along with a small amount of 1,4-addition product **243**. As can be expected from such a complicated reaction it is hard to extrapolate any precise data from the crude ¹H NMR, however, it is clear that there was poor selectivity. The ratio of diastereoisomers **241** was 2:1 (*syn/anti:anti/anti*). Presumably **243** originates from degradation of the *syn/syn*-nitroamine (as has been observed previously during trifluoroacetate protection of this diastereoisomer). Interestingly, only a single diastereoisomer of pyrrolidone **242-a** was formed (**Scheme 89**). The

stereochemistry of pyrrolidone **242-a** corresponds to the open chain *syn/anti*-diastereoisomer, ignoring possible epimerisation of the nitro stereocentre.

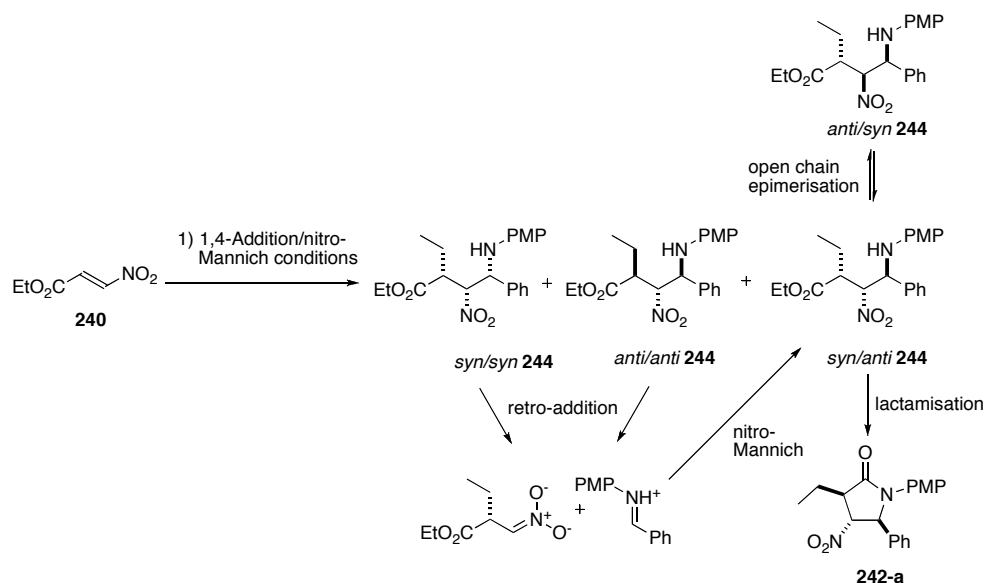


Scheme 89: One pot 1,4-addition/nitro-Mannich/lactamisation

When the reaction was repeated under the standard conditions developed using Et₂O (2 h at - 78 °C then rt for a further 1 h) the same diastereoisomer of pyrrolidone **242-a** was isolated as a single isomer (in 63 %).⁹³ Presumably the series of events leading to pyrrolidone **242-a** is 1,4-addition/nitro-Mannich/lactamisation. This leads to the question why is only one diastereoisomer of **242-a** observed when three acyclic diastereoisomers are produced under the reaction conditions (**Scheme 89**). Firstly it should be noted that if the reaction in THF was repeated under identical conditions except for the time left at rt after the addition of imine and TFA (increased from 5 min to 8 h) a yield of 53 % of pyrrolidone **242-a** was obtained as the only isolated product.

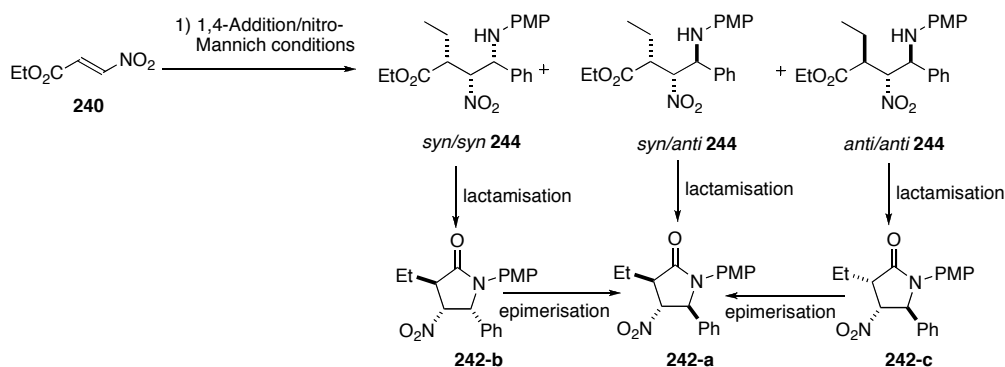
The fact that a single diastereoisomer of **242-a** was observed can be explained in two ways. Firstly, it could be that only a single diastereoisomer of the open-chain β-nitroamine (*syn/anti*-β-nitroamine **244**) cyclises. The other diastereoisomers of **244** could be gradually converted into the *syn/anti*-β-nitroamine **244** via a retro-addition/nitro-Mannich mechanism, and from there into **242-a** via lactamisation (**Scheme 90**). If we look at the results of the 2 THF experiments performed, we can see that in the second 8 h experiment a yield of 53 % of **242-a** was isolated. From the first experiment (**Scheme 89**) the yield of

242-a was 16 %, along with 37 % of a 2:1 mixture of *syn/anti:anti/anti-244*. This suggests that there was only 24 % of the *syn/anti*-diastereoisomer remaining that could cyclise to form the pyrrolidone **242-a**, which would only give a maximum 40 % combined yield. As 53 % was isolated in the longer experiment, it would seem that at least one of the remaining diastereoisomers must be converted into pyrrolidone **242-a** over time. Although *anti/syn 242-a* has not been isolated, either in this series or any other, it is possible that this diastereoisomer is also formed. Epimerisation of the nitro stereocentre prior to cyclisation (through either an acidic or basic mechanism) would provide *syn/anti 244*, whilst epimerisation after cyclisation would provide the observed stereochemistry of pyrrolidone **242-a**. We believe that both of these possibilities would be minor pathways and, due to the lack of evidence for the formation of *anti/syn* diastereoisomer, will no longer consider this diastereoisomer in future discussions.



Scheme 90: Proposed mechanism for the formation of **242-a** as a single diastereoisomer

The second possibility is that all three observed diastereoisomers of **244** cyclise, and then undergo epimerisation of the appropriate stereocentres to form pyrrolidone **242-a** (**Scheme 91**). Both mechanisms will be dealt with in turn, and the advantages and shortcomings of both discussed.



Scheme 91: Alternative mechanism for the formation of **242-a** as a single diastereoisomer

The mechanism shown in **Scheme 90** poses two questions. Firstly, is the suggested mechanism for the retro-addition/forward addition a possible pathway for the conversion of β -nitroamines *syn/syn* and *anti/anti*-**244** into the required *syn/anti*-form? As has been shown in **Table 11**, the diastereoselectivity of the reaction is highly dependent on the time the reaction was stirred at ambient temperature. At longer reaction times at ambient, the ratio of *syn/anti*:*syn/syn* increased in favour of the *syn/syn* diastereoisomer (**Table 11**, entries 2, 3, 5 and 6). As the reaction conditions are not basic in nature it is hard to believe this change in diastereoselectivity arose through a deprotonation/reprotonation epimerisation mechanism. There is also an acid catalysed pathway of epimerisation, *via* tautomerisation to the nitronic acid form (similar to the keto-enol tautomerisation); however, we believe the acid catalysed retro-addition pathway is a faster process. This also explains why the yield of **242-a** increases over time. As *syn/anti*-**244** is converted to **242-a** the equilibrium position of the

diastereomeric ratio is affected (the cyclisation is most probably irreversible under the reaction conditions), thus over time all diastereoisomers are transformed into *syn/anti*-**244** and from there into **242-a**. This explanation relies upon only one diastereoisomer undergoing lactamisation. This could be explained if we assume the activation energy for the pathway leading to lactamisation from *syn/anti*-**244** to **242-a** must be lower than for the corresponding pathways from the other diastereoisomers (*i.e.* kinetic control). If we look at the three dimensional conformation of the three diastereomeric tetrahedral intermediates leading up to pyrrolidones **242-a**, **242-b** and **242-c** (**Figure 21**) we can see that intermediate **242-aa** has all three substituents in *pseudo*-equatorial positions when in conformation **242-ab**. This conformation minimises all *pseudo*-1,3-diaxial interactions, and thus represents an energy minimum. The remaining intermediates have either one (**242-cc**) or two (**242-bc**, **242-bb** and **242cb**) *pseudo*-1,3-diaxial interactions, and thus incur an energy penalty. If one assumes the transition state resembles the energy minimised conformation of the intermediate, it is a fair assumption that the transition state leading to conformation **242aa** will be the lowest in energy and thus formed preferentially. This would explain the presence of only one diastereoisomer of the pyrrolidone. In this analysis the configuration of the carbonyl and OEt substituents will have little effect on the relative energies of the corresponding transition states (approximating the carbonyl oxygen to have a similar value to a hydroxyl, *A*-values OH = 0.60, OMe = 0.58 kcal/mol).¹⁰⁶

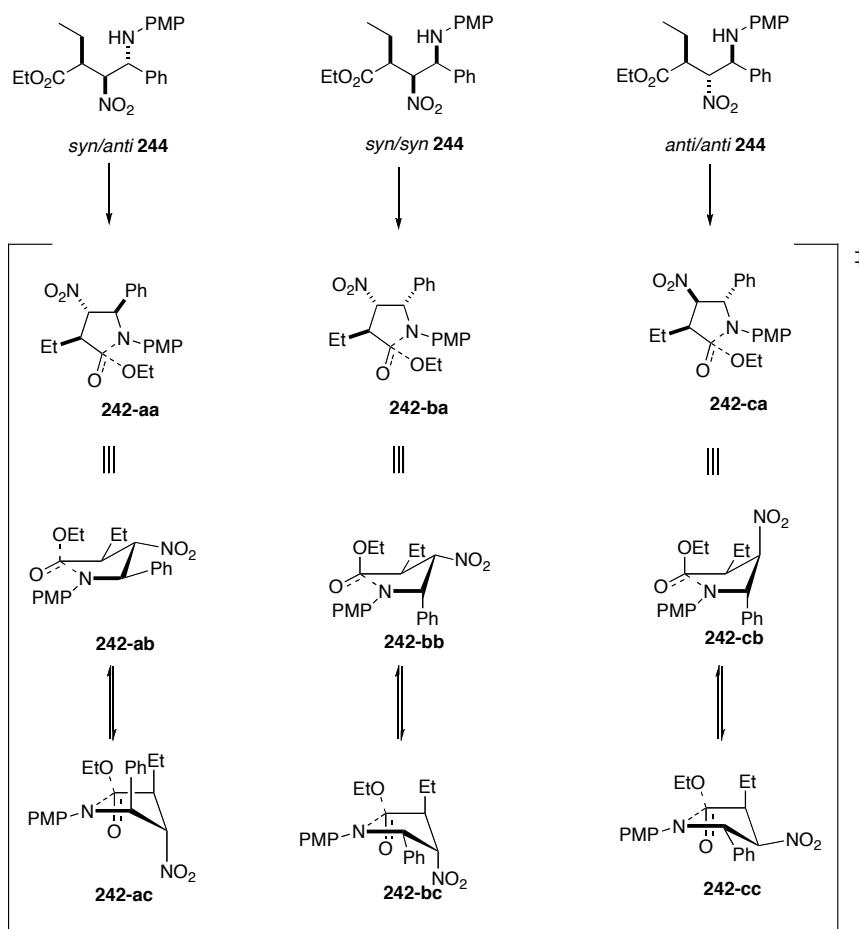
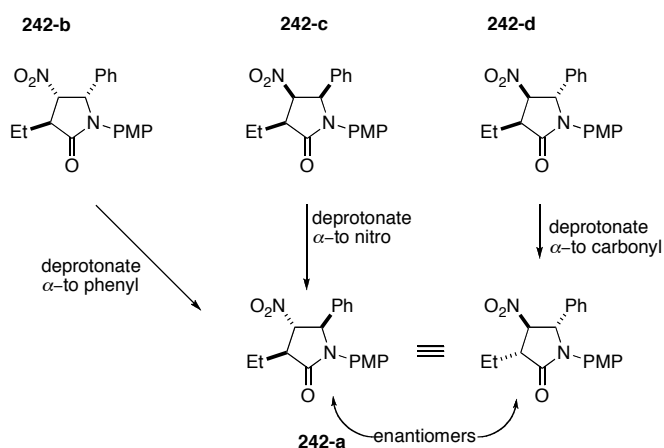


Figure 21: Conformational analysis of tetrahedral intermediates leading to pyrrolidinones **242-a**, **242-b** and **242-c**

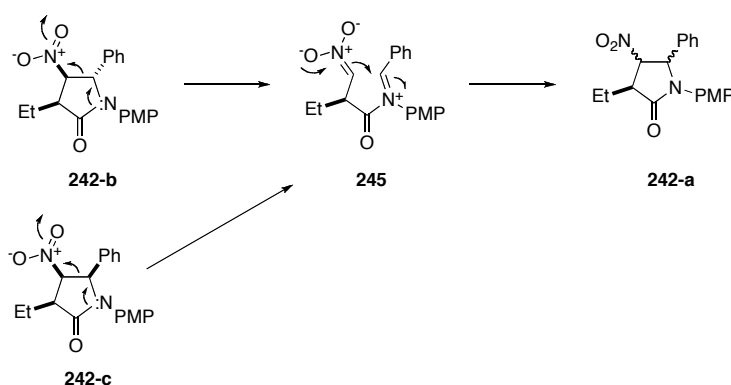
The alternate mechanism would require a reasonable mechanism to explain the epimerisation of the required stereocentres of **242-b** and **242-c** into those of **242-a** and, if there is a mechanism, will this favour the stereochemistry of **242-a**? Conformation **242-ab** is the lowest energy arrangement of the groups around the ring. If a mechanism for epimerisation exists, it would be a safe assumption to assume that over time the thermodynamically more stable, all equatorial product would be preferred. During the reaction an ethoxide anion is generated upon lactamisation. This base should be strong enough to deprotonate α - to a nitro

group (converting unseen **242-d** into **242-a**). However, it is unlikely to be able to deprotonate α - to the lactam carbonyl (required to convert **242-c** into **242-a**) or α - to the phenyl (required to convert **242-b** into **242-a**).



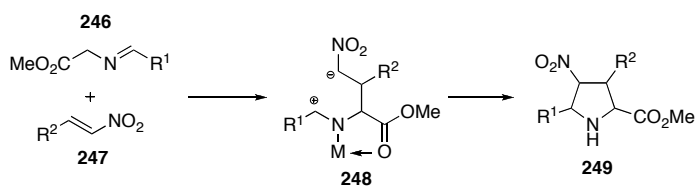
Scheme 92: Discounted deprotonation mechanism

An alternative mechanism for the required epimerisation of **242-b** and **242-c** could involve a retro-addition of **242-b** and **242-c** to give the same intermediate **245** followed by forward addition to regenerate the pyrrolidone with scrambled stereocentres (**Scheme 93**). As the ethyl stereocentre remains fixed, this could control the resulting stereocentres of the forward reaction. As pyrrolidone **242-a** is the thermodynamic product (*vide supra*), presumably this would predominate over time.



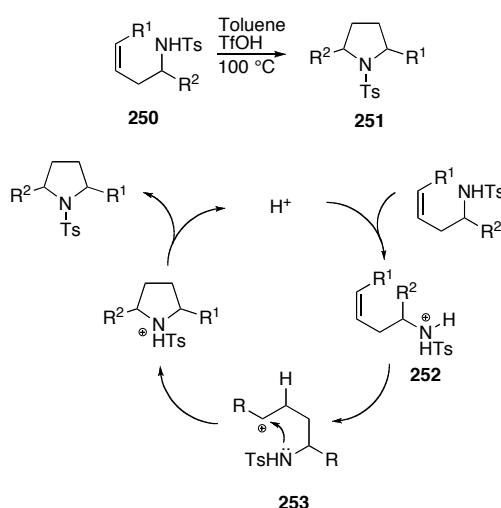
Scheme 93: Alternate mechanism for epimerisation

As the pyrrolidone is still a β -nitroamine, there is still the possibility of a retro-nitro-Mannich reaction. The iminium ion **245** thus formed may then undergo a forward nitro-Mannich cyclisation. Formally this is a 5-endo-trig process, which only occur under special circumstances. In this case carbocationic character at the benzylic iminium centre may facilitate this process. There is some literature precedent for this type of process, including two closely related examples within the nitro-Mannich literature (**Scheme 29** and **Scheme 94**). Two groups have reported the formal [3+2] cycloaddition of azomethine ylides **246** to nitro alkenes **247**, and both reactions operate upon the same principle.^{35, 111} In these cases formation of a benzylic carbocation was presumed to assist the process.



Scheme 94: Formal [3+2] cycloaddition of azomethine ylide **246** to nitro alkene **247**¹¹¹

The formation of a stabilised cation to aid 5-*endo-trig* processes is not limited to the nitro-Mannich literature. During the acid catalysed synthesis of pyrrolidines Hartwig *et al.* observed a similar process (**Scheme 95**).¹¹² A selection of homoallylic sulfonamides **250** underwent cyclisation to furnish the substituted pyrrolidines **251** in excellent yields. The authors propose protonation of the tosylamide (on either nitrogen or the tosyl oxygen, **252**) followed by intramolecular proton transfer to the double bond to generate cationic intermediate **253**. Cyclisation onto the cation and proton transfer completes the catalytic cycle.



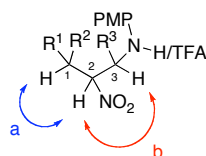
Scheme 95: Proposed acid catalysed cycle for 5-*endo-trig* cyclisation of homoallylic sulfonamides **250**

With this literature precedent we are confident that the forward reaction is a feasible pathway. The stereochemical result of the forward reaction would be controlled by the only remaining stereocentre, the ethyl group. As pyrrolidone **242-a** represents the thermodynamic product (**Figure 21**), we expect this diastereoisomer to predominate over time. There are, however, some major objections to this mechanism. Firstly, as has been shown with the

trifluoroacetamides, a β -nitroamine with the lone pair of the nitrogen delocalised into a carbonyl system is far less likely to undergo retro-addition than one that does not have this extra stabilisation. When the reaction was carried out under the standard conditions developed for THF (**Scheme 89**) the lactamisation proceeded to approximately 50 % (based on residual acyclic diastereoisomers). Whilst all three acyclic diastereoisomers were present, only a single pyrrolidinone was observed. Unless the epimerisation of the cyclic products is instantaneous and 100 % selective for formation of **242-a** some of the other diastereoisomers would be expected. This observation, therefore, implies that the first suggested mechanism, involving lactamisation of only one diastereoisomer *via* the lowest energy pathway, is more likely than the second retro-nitro-Mannich/recyclisation pathway.

2.4 Confirmation of Stereochemical Assignment

As has been demonstrated, we have developed and optimised a reaction that, depending on the choice of solvent, can provide a choice of two diastereoisomers. The rationale behind this unexpected, solvent dependent diastereoselectivity will be explained later (see section 2.5). Whilst several of the examples have been crystallised as single crystals of sufficient quality to provide x-ray diffraction crystal structures (see appendix C), this has not been the case for all the analogues. We believed, therefore, that a simple way to confirm the obtained stereochemistry would be to take a closer look at the *J* values for pertinent signals from the ^1H NMR spectra of the analogues, and see if these could be used to differentiate the different diastereoisomers (see appendix B). The signals to be inspected are those between the 1,4-addition centre and the nitro group (a, scheme above **Table 17**), and between the nitro group and the amino centre (b, scheme above **Table 17**). In all cases R_1 refers to the group originating from the nitro-alkene and R_2 refers to the group originating from the zinc reagent.

Table 17: Summary of coupling constants from Appendix B

Entry	General structure	Range a (Hz)	Range b (Hz)
1		10.6-11.6	3.2-4.1
2		10.5-11.6	3.2-4.1
3		3.2-5.4	9.9-11.7
4		7.2-8.7	5.7-7.2
5		8.7-9.1	8.7-8.7
6		5.3-5.7	7.9-8.0

Pleasingly, the vast majority of the various sub sets fall within a narrow range (< 2 Hz) for all the members of the sub set (with two exceptions, *vide infra*). Surprisingly, it would seem that the presence or absence of the trifluoroacetamide protecting group has a much larger influence on the magnitude of the coupling constant than the relative stereochemistry. Entries 1 and 2, containing the same relative stereochemistry between C_1 - C_2 , but differing between the nitro-Mannich centres C_2 - C_3 , show very similar values, to the extent that it is impossible to distinguish between these two diastereoisomer based on J values alone. There was, however, a distinctive change in chemical shift between the ^1H NMR shifts for these compounds that allows for the diastereoisomers to be distinguished (entry 1 CHN proton ~ 4 ppm, entry 2 CHN proton ~ 5 ppm). There was a major change in coupling constant b , however, between the free amine and the protected trifluoroacetamide species and perhaps this is an indication of a major conformational change between the protected and non-protected species for the *anti*- β -nitroamines. It has been proposed that β -nitroamines can exist in a hydrogen bonded chair conformation (**Figure 22**). If the amine was protected as the trifluoroacetamide, this hydrogen bonding is no longer available, and perhaps this explains the dramatic shift in J values between the protected and unprotected *syn/anti*- β -nitroamines/trifluoroacetamides. In the protected case opposition of dipoles may dictate the conformation of the system. The *anti*- β -nitroamines have an axial and an equatorial proton whilst in the hydrogen bonded chair conformation **254**. This relates to a dihedral angle of 60° , which, according to the Karplus equation, should have a medium J value. If the hydrogen bonded network is no longer available (*i.e.* the amine is protected), the conformational preference may be altered to reduce the molecules overall dipole, and we can expect a major contribution from structure **255**. This conformation has a dihedral angle of 180° , which should have a larger J value, and this is in agreement with the experimental data.

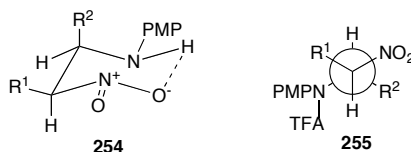


Figure 22: Possible hydrogen-bonded β -nitroamine **254** and non hydrogen bonded β -nitro-trifluoroacetamide **255**

As was mentioned earlier, there were two exceptions where the coupling constants fell some way outside of the expected range for the analogues in that particular subset (**Table 17**, entry 3). These exceptions have the 2-furyl and 2-thiophenyl groups on the amino stereocentre (**Figure 23**). The observed values are much higher than expected (~ 8 Hz, see Appendix B). Fortunately we were able to obtain a crystal structure for the 2-furyl analogue **256**, which confirms the relative stereochemistry is as shown. As both structures are closely related, and the coupling constants for these two analogues are in line with each other, we propose that 2-thiophenyl analogue **257** also contains the expected *syn/anti*-stereochemistry. As it seems that this analysis can provide little information as to which diastereoisomer is present no more attention was given to this line of enquiry. The next section will discuss the origins of this diastereoselectivity.

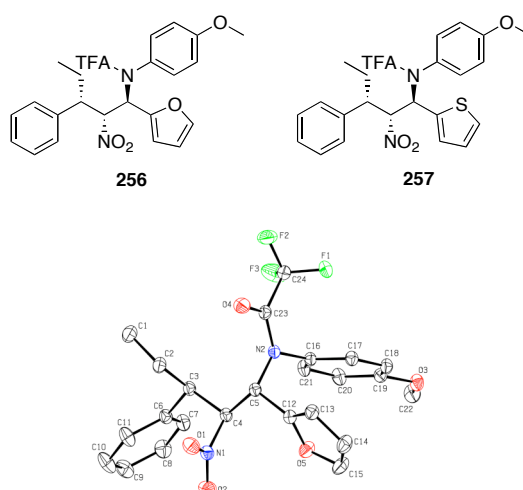


Figure 23: The two structures with J values falling outside the expected range, and the crystal structure for the 2-furyl analogue **256**

2.5 Origins of Diastereoselectivity

The previous sections have demonstrated that relative stereocontrol across all three centres in the 1,4-addition/nitro-Mannich reaction is possible, and in fact tuneable by solvent choice. In light of this we felt it was important to rationalise this stereocontrol in order to predict the diastereoselectivity of any future reactions, and to perhaps provide an explanation for the unusual *syn*-stereochemistry across the nitro-Mannich centres when the reaction solvent was Et₂O. In the system there are two pairs of stereocentres to consider. First is the relative stereochemistry between the nucleophile (usually an ethyl group) and the nitro group (C₁-C₂, **Figure 24**), and secondly that between the nitro group and the amine resulting from the nitro-Mannich portion of the reaction (C₂-C₃, **Figure 24**). For both the reactions in Et₂O and THF the relative stereochemistry for the major products across C₁-C₂ is the same. This is perhaps an indication that the reactive nitronate conformation is the same in both cases. The difference comes when the nitro-Mannich stereocentres (C₂-C₃) are involved, and we believe that this is an indication of the reaction proceeding *via* different transition states in the different solvents.

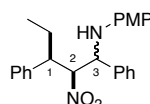
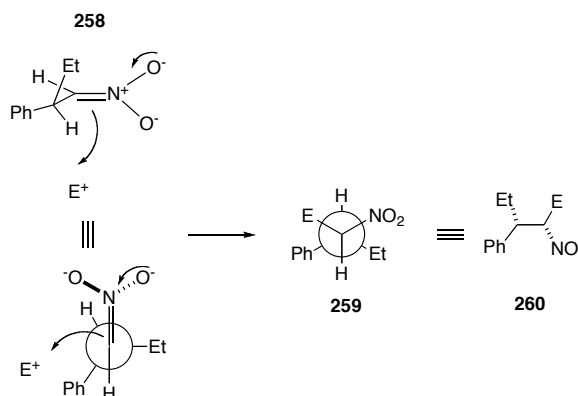


Figure 24: The two pairs of stereocentres

2.5.1 Nitronate Conformation

As the C₁-C₂ stereocentres are identical for both major diastereoisomers in both solvents, this element will be examined first. As was shown in the introduction (see section 1.4), a number of general rules for the electrophilic attack α - to a stereocentre exist. We will now attempt to rationalise the results of this research program by applying the model described in section 1.4 to our own system. Whilst it has been shown that electronic effects can complicate the system, we will assume that, in the absence of heteroatoms on the chiral centre, the diastereoselectivity is dictated by the sterics of the stereocentre. The first task is to assign the steric sizing of the groups involved. We will initially look at the model proposed by Fleming.⁸⁴ As Fleming has pointed out,⁸⁵ the ranking of groups in these types of systems is not a simple task, as the amount of steric hindrance one group offers relative to another depends on the electronic nature, size, shape and the approach angle of the electrophile. Fleming also suggests that *A*-values are an unreliable measure of size for the systems he investigated, and thus utilises Sternhell's parameter. Due to this we will use Sternhell's parameter as the defining scale for ranking the groups whilst employing this model. So, using the model described in the introduction to predict the diastereoselectivity of the model system (**Scheme 85**), we rank the groups as S = H, M = Ph and L = Et. In this case we have ranked ethyl as larger than phenyl. Whilst the data for Sternhell's parameter for an ethyl is not available, based on the fact that a methyl group is classed as larger than a phenyl (methyl = 1.8 vs Ph = 1.6 Å),⁸⁷ we assume that the ethyl group can be considered as larger than a phenyl. Placing the large group *anti*- to the incoming electrophile (initially we will look only at the first two stereocentres, and the imine electrophile will be represented as E⁺), and the proton residing in the sterically more demanding inside position results in predicted reactive conformation **258**. After the electrophilic attack takes place the resultant stereochemistry would be as in

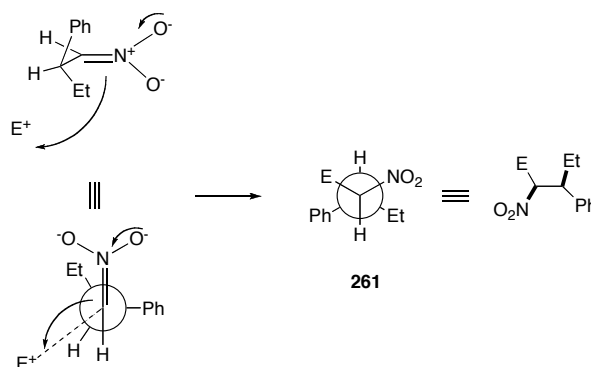
Newman projection **259**. If this projection is rotated into the plane we can see that product **260** possesses a *syn*-relationship with respect to the ethyl and nitro groups, which was the experimentally observed relationship.



Scheme 96: Predicted reactive conformation and resultant stereochemistry based on Fleming's model

Whilst this model is extremely simplistic in its approach to understanding the relative stereochemistry, it does at least offer a solution to the question of the observed diastereoselectivity for the major products in both reaction media possessing the *syn*-stereochemistry. Obviously the result only holds if Sternhell's parameter is used. If the size ranking of the ethyl and phenyl is based on *A*-values the model predicts the major products should have an *anti*-relationship across these two centres. With this in mind, we will now consider the second model, Houk's "outside crowded" model.⁹² As was shown in the introduction (**Scheme 70**), this model correctly predicts the diastereoselectivity for a nitro-Mannich reaction with an α -stereocentre. In this case, the groups are ranked in the more familiar order of $S = H$, $M = Et$ and $L = Ph$, based on *A*-values. If we then apply the model, *i.e.* the phenyl *anti*- to the incoming electrophile, the ethyl in the sterically less demanding inside position and the proton in the crowded outside position, and follow the reaction through the

resulting Newman projection **261** shows the stereochemistry is as observed, *i.e.* *syn*- between the nitro and ethyl groups (**Scheme 97**). With the precedent of this model correctly predicting the result of a separate nitro-Mannich reaction, we currently favour this model over Fleming's.



Scheme 97: Predicted reactive conformation and resultant stereochemistry based on Houk's model

With the previously detailed most likely reactive conformation of the nitronate justified, attention now shifted to the C₂-C₃ pair of stereocentres across the nitro-Mannich centres. As in this case the relative stereochemistry is different in the differing reaction solvents, we will handle both reactions separately, as we believe different transition states are in operation for each solvent. As was noted earlier, the reaction mixtures were homogeneous when THF was used as the solvent, but heterogeneous when the solvent was Et₂O. A sample of the white precipitate was isolated, and shown to be zinc trifluoroacetate by comparison with an authentic sample.⁹³ We believe this difference in the reaction mixture allows the reaction to proceed *via* different transition states, and accounts for the reversal of selectivity across the nitro-Mannich centres (C₂-C₃).

2.5.2 Homogeneous Reactions In Tetrahydrofuran

When using THF, the relative stereochemistry across the nitro-Mannich centres was *anti*. We have previously justified this diastereoselectivity to the reaction proceeding *via* a closed Zimmerman-Traxler like cyclic transition state (*cf.* aldol and Henry reactions) with a metal ion coordinating to both the nitronate and the imine (**Figure 25**).¹⁹ In this present case the metal in solution is the Zn^{2+} ion. If we assume the imine remains in the (*E*)-geometry, the imine substituents (on both carbon and nitrogen) are forced to adopt *pseudo*-axial positions due to the geometric constraints of having a metal coordinating to the lone pair of the imine nitrogen and the O^- of the nitronate (**Figure 25**). The final variable is the orientation of the side chain (R, **Figure 25**). Positioning the side chain in the more favourable *pseudo*-equatorial position results in **262-a**, and results in an *anti*-relationship across the nitro-Mannich centres, whilst placement of the side chain in the higher energy *pseudo*-axial position results in **262-b** and a *syn* relationship.

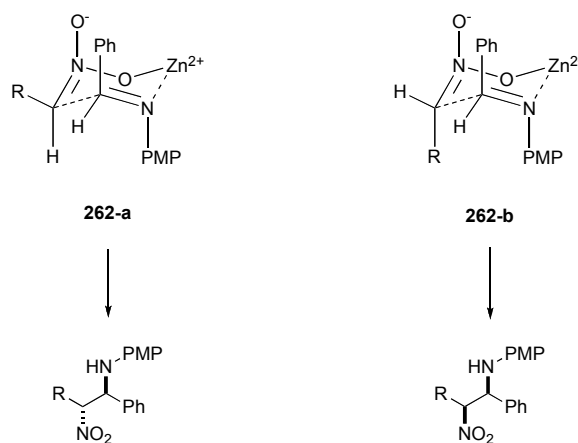
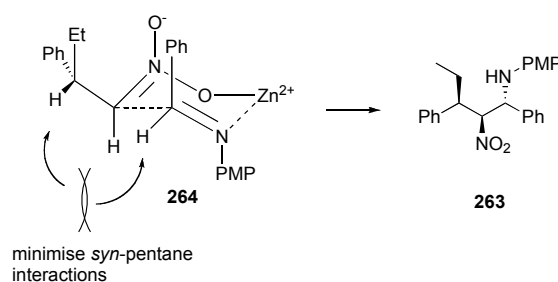


Figure 25: Two possible Zimmerman-Traxler like transition states

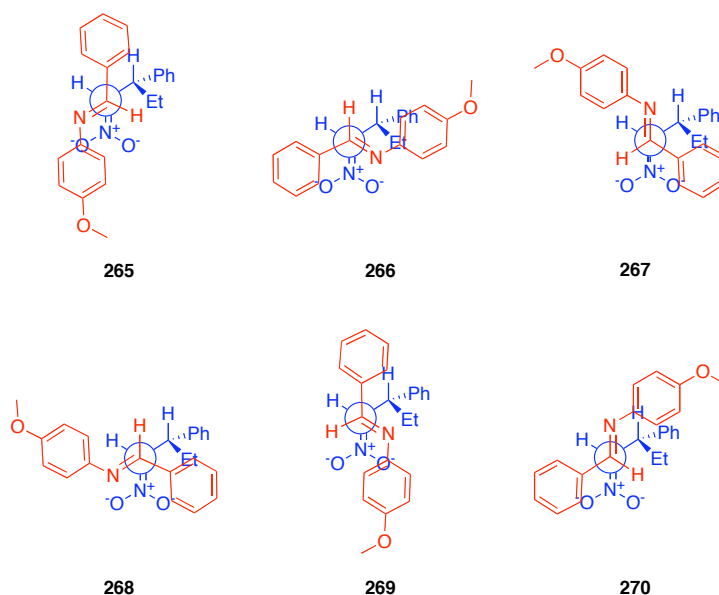
Due to the unfavourable 1,3-diaxial interaction between the side chain and the PMP protecting group in **262-b**, we would suggest that **262-a** is the lower energy transition state. This explains not only the observed *anti*-relationship, but also why the reaction times have such an effect on the diastereoselectivity. The diastereoselectivity for the reaction in THF is at its peak 5 min after removing the vessel from the cold bath (entry 2, **Table 11**). If the reaction is left for longer at rt the diastereoselectivity drops until after 16 h the *syn/anti:syn/syn* ratio is 1:1 (entry 6, **Table 11**). Presumably the reaction is under kinetic control at low temperatures, but at higher temperatures becomes reversible and operates under thermodynamic control, thus over time the amount of the thermodynamically more stable *syn*-nitro-Mannich product increases (*syn*-nitroamines in a hydrogen bonded chair can align all substituents in an equatorial position). If the preferred conformation of the nitronate side chain is now taken into account (*i.e.* with the large phenyl group *anti*- to the imine, and the small proton occupying the outside position), we can imagine the transition state for the reaction resembles **264** (**Scheme 98**). As can be seen from **264** the conformation of the nitronate side chain also minimises *syn*-pentane interactions between the substituents on the imine and on the side chain, the two interactions being H-H and Et-Ph.



Scheme 98: Lowest energy transition state for formation of *syn/anti*-**263**

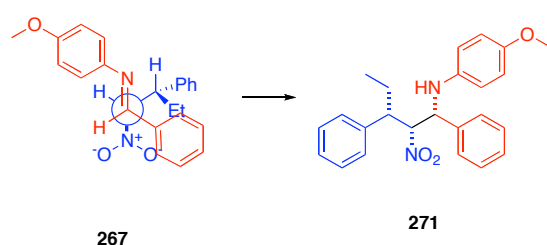
2.5.3 Heterogeneous Reactions In Diethyl Ether

When the reaction solvent is THF, the Zn^{2+} ions are in solution, and therefore able to co-ordinate to the nitronate and the imine, creating a cyclic transition state. If, however, the reaction solvent used is Et_2O , the zinc trifluoroacetate precipitates, and is therefore not present to co-ordinate to the reactants and create the cyclic transition state. In this case we believe the reaction could proceed through an open transition state. If we again assume the imine remains fixed in the *E* geometry, and we discount eclipsed transition structures based on steric grounds,¹¹³ their remain only six possible transition states (**Scheme 99**). These are obtained from the nitronate (with the side chain in the preferred conformation discussed previously) approaching either face of the imine in each of the three staggered conformations.



Scheme 99: Possible open transition states

Taking the simplistic view of the situation, we can make the assumption that the transition states with more unfavourable steric and electronic interactions will be of a higher energy than those with fewer interactions. Transition states **266** and **268** can immediately be disregarded due to the large *syn*-pentane interaction between the ethyl of the side chain and the phenyl of the imine. Transition states **265** and **269** look promising in terms of minimising steric interactions, however, these conformations have unfavourable dipole-dipole interactions between the parallel N=C imine bond and the N-O⁻ nitronate bond. Transition states **267** and **270** have both C=N bonds arranged in a linear fashion with respect to the nitronate group, which is a much more favourable arrangement. Finally, transition state **270** has a steric clash between the PMP protecting group and the nitronate side chain, whereas **267** has a much less sterically congested arrangement. We believe, therefore, that **267** represents the sterically and electronically most favourable open transition state. If the reaction from transition state **267** is followed through the diastereoselectivity predicted is that observed in the reaction, *i.e.* *syn/syn*-**271** (Scheme 100).



Scheme 100: Resultant *syn*-stereochemistry ensuing from transition state **267**

If the product resulting from transition state **270**, which we propose is the next lowest in energy, due to the linear flow of charge and minimisation of steric clashes, is considered, we see that this corresponds to the second most populous diastereoisomer from the Et₂O reaction, *syn/anti*- β -nitroamine **263**. This may allow us to draw some conclusions regarding the diastereoselectivity. It is

possible that the loss of selectivity across the nitro-Mannich centres is due to either the reaction proceeding through a closed transition state (of which **262-a**, **Scheme 98** is proposed to be the lowest in energy) due to the presence of trace amounts of Zn^{2+} in solution, or through a second, slightly higher energy, open transition state.

The previous section has attempted to explain the observed diastereoselectivity encountered during this research. Whilst the models provided make a number of assumptions, we believe these are reasonable, and have allowed us to devise a working hypothesis on which to base future reactions.

Chapter 3:

Future Work & Conclusions

Future Studies and Conclusions

3.1 Future Studies

The previous chapter discussed the research carried out towards a one-pot 1,4-addition/nitro-Mannich reaction. Whilst a significant amount of progress towards this reaction was achieved, like all areas of research, there is still plenty of work to be carried out. This chapter will outline the work that, due to time constraints, was not carried out during the course of this PhD. This work can be split into two distinct sections. The first to be discussed will be reactions designed to probe the stereochemical model of the reaction. The second area will be the use of alternative reagents to provide access to a larger, synthetically more useful range of nitro-Mannich products.

3.1.1 Confirmation of Stereochemical Model

In the previous chapter (see section 2.5) two models were described in an attempt to explain the observed stereochemistry of the electrophilic addition to the nitronate. One model, based on the work of Fleming *et al.*⁸⁴ described as an “inside crowded” model, requires the steric ranking of the different groups to be ordered using Sternhell’s parameter. The second model, based on the work of Houk *et al.*⁹² described as an “outside crowded” model, requires the steric ranking of the different groups to be ordered using the more familiar *A*-values. Both models correctly predict the stereochemistry observed in the molecules synthesised so far, however, due to the different order the two steric parameters

rank different groups, it could be possible to discount one of the models by determining the relative stereochemistry of two more products (**Figure 26**).

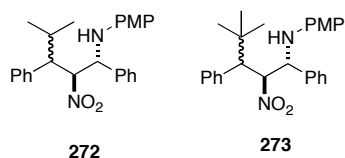


Figure 26: Products to be synthesised to investigate the stereochemical models

Table 18 lists the experimentally determined values for a number of groups for *A*-values and Sternhell's parameter. As can be seen, for Sternhell's parameter, the effective size runs $\text{Ph} < \text{Me} < {}^i\text{Pr} < {}^t\text{Bu}$. For *A*-values, the order runs $\text{Me} < {}^i\text{Pr} < \text{Ph} < {}^t\text{Bu}$. So, if the nitronate conformation is controlled by a system where *A*-values are an appropriate measure of size, the relative stereochemistry of the major diastereoisomer of **272** should be *syn/anti*. This is the same relative stereochemistry as previously observed for the methyl and ethyl products, and would fit in with the ranking order shown in **Table 18**, where Ph would be considered the large group, and Me, Et or *i*Pr are considered to be the medium group. The relative stereochemistry of the major diastereoisomer of **273**, however, should be *anti/anti*, as in this case *t*Bu is considered the large group and Ph the medium group. If, however, the stereochemistry of both **272** and **273** is *syn/anti*, we can discount *A*-values as a measure of size for this system. The synthesis of **272** and **273** can be achieved by the addition of diisopropyl zinc or ditert-butylzinc to β -nitrostyrene, however, these reagents are expensive, and have low reactivity. A much simpler way to synthesise these products would be the addition of diphenylzinc to the appropriate alkyl nitro-alkene. This study ignores the possibility of an electronic effect, however, we believe this will not be an issue unless the stereocentre contains a heteroatom, at which point alternate models may control the stereochemistry (see section 1.4).

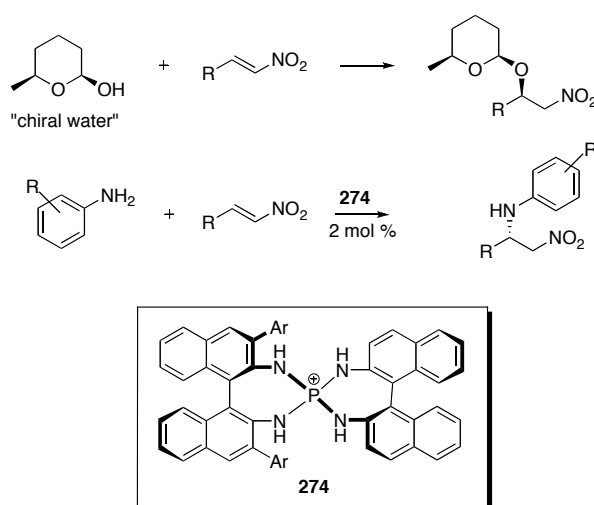
Table 18: List of *A*-values and Sternhell's parameter for a selection of groups

Increasing steric bulk	<i>A</i> -values (kcal/mol)	Sternhell's Parameter (Å)
Small	Me (1.70)	Ph (1.62)
	ⁱ Pr (2.15)	Me (1.80)
	Ph (3.00)	ⁱ Pr (2.2)
Large	^t Bu (4.50)	^t Bu (3.6)

3.1.2 The Use of Alternate Nucleophiles and Heteroatoms

The next area of future work concerns the use of a wider range of reagents. Whilst we believe the previously described 1,4-addition/nitro-Mannich reaction represents a major advance in the field, it is still of limited synthetic use. Whilst there is much literature pertaining to the synthesis and use of functionalised dialkylzinc reagents, the synthesis of these reagents can be laborious and the resulting reagents are often far less reactive than diethylzinc. This, combined with the limited availability of commercial dialkylzinc reagents represents a major limitation of the methodology. The simplest way round this is to use Grignard reagents, for which a very large range of commercial reagents is available, and an even larger range can be made through simple reactions. Their main drawback, of course, is that their enhanced reactivity makes the 1,4-additions extremely hard to control in an asymmetric fashion. One way to achieve stereoselectivity would be to use one of the methods detailed in the introduction (see section 1.3)

Another interesting possibility is the large number of heteroatom reagents that are known to add to nitro-alkenes in an asymmetric fashion. Of the most interest would be the “chiral water” reagent, developed by Dixon *et al.*¹¹⁴ and a chiral Brønsted acid promoted azamichael addition developed by Ooi *et al.*¹¹⁵ (**Scheme 101**). If these methodologies could be included into a 1,4-addition/nitro-Mannich reaction sequence the resultant products could provide a wealth of varied functionality amiable to synthesis.



Scheme 101: “Chiral water” and chiral Brønsted acid promoted aza michael additions to nitro-alkenes

3.2 Conclusions

During the course of this doctoral research the chemistry of the nitro-alkene motif has been exploited twice, firstly as a Michael acceptor, and secondly, in a related manner, as a latent nucleophile. The research initially looked at the addition of cyanide to nitro-alkenes, a surprising gap in the literature. A number of reagents were investigated, namely TMS-CN, $K_4[Fe(CN)_6]$ and acetone

cyanohydrin. It was shown that TMS-CN would only undergo conjugate addition of cyanide to nitro-alkenes in the presence of a catalytic amount of KCN/18-crown-6 complex, and only at low conversions. Similar conditions, but using acetone cyanohydrin as the stoichiometric cyanide source, were developed that underwent 1,4-addition of cyanide to nitro-alkenes in high yield, however, the conditions were unsuitable for a one-pot 1,4-addition/nitro-Mannich protocol, presumably due to the formation of HCN under the reaction conditions. The reaction is also unsuitable for aromatic substituted nitro-alkenes. The lack of a general procedure for the addition of cyanide to nitro-alkenes, however, led us to optimise this reaction, and demonstrate the synthetic versatility of the resultant products. Finally, another cyanide source, $K_4[Fe(CN)_6]$, was investigated. In this case the product observed was not the desired 1,4-addition product, but a cyclisation product. We propose that 1,4-addition is involved in the mechanism, however further optimisation was not attempted. The final section details the use of dialkylzinc reagents as a trigger for the one-pot 1,4-addition/nitro-Mannich reaction. The reaction was found to be high yielding, diastereoselective (if the substrate is a β -nitrostyrene) and has a wide scope in terms of the nitro-alkene, the imine and the dialkylzinc reagent. The diastereoselectivity was found to be tunable by the choice of solvent, and a hypothesis was proposed to account for the observed diastereoselectivity. Finally, we were able to render the reaction enantioselective by the use of existing chiral technology,^{61, 62}

Chapter 4:

Experimental

Experimental

4.1 General Experimental Details

For all non-aqueous chemistry, glassware was rigorously flame-dried under a stream of nitrogen. Cryogenic conditions ($-78\text{ }^{\circ}\text{C}$) were achieved using solid CO_2 /acetone baths, temperatures of $0\text{ }^{\circ}\text{C}$ were obtained by means of an ice bath. All reaction temperatures refer to values recorded for an external bath. Room temperature implies temperatures in the range $20\text{--}25\text{ }^{\circ}\text{C}$. Petrol refers to petroleum ether ($40\text{--}60\text{ }^{\circ}\text{C}$ fraction).

Reaction progress was monitored by thin layer chromatography (TLC) performed on Poligram SIL G/UV254 plastic backed plates, which were visualised by a combination of ultraviolet light (254 nm) and visualising dips (anisaldehyde and potassium permanganate). Column chromatography was performed using BDH 60 silica gel in the indicated solvent.

^1H NMR and ^{13}C NMR spectra were recorded using Bruker DPX400, AV400 AV(III)400 and AV500 spectrometers at 298 K in CDCl_3 unless otherwise stated. Chemical shifts are given in ppm downfield from tetramethylsilane, using residual protic solvent as an internal standard ($\delta = 7.27\text{ (CDCl}_3\text{)}$). J values are reported in Hz and rounded to the nearest 0.1 Hz and are uncorrected. Multiplicities for coupled signals are as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (sept) septet, (oct) octet, (apt) apparent, (br) broad (dd) double doublet *etc.* ^{19}F NMR spectra were measured using Bruker DX300 and AV400 spectrometers, referenced to trichlorofluoromethane. Mass spectromeric data were obtained using a VG Micromass 70E spectrometer, using

electron impact (EI), a Thermo Finnigan mat900xp, using electron impact or chemical ionisation (EI and CI), a vg70-se, using fast atom bombardment (FAB) and a Waters LCT premier xe, using electrospray ionisation. Results for high-resolution mass spectrometry (HRMS) are quoted to four decimal places. Melting points were recorded on a Stuart Scientific SMP3 system and are uncorrected. Infrared spectroscopy was recorded on a Perkin Elmer 1600 FTIR instrument in dichloromethane or as a thin film unless noted, and are reported in cm^{-1} . Elemental analyses were acquired on a Hewlett Packard 1100 series system. HPLC analysis was acquired with a Hewlett Packard Capillary HP4890A GC analyser using the indicated HPLC column and solvent system. Optical rotations were recorded on a Jasco DIP370 Digital Polarimeter at the temperature indicated and are reported in $\text{deg cm}^2 \text{g}^{-1}$. Where a number of literature compounds were synthesised *via* the same method only a single representative example is given. All novel compounds are reported with full spectroscopic data. Where a literature compound has been synthesised *via* a novel route only the melting point (where appropriate) and ^1H NMR data are reported. Where reported, ratios refer to *syn/anti:syn/syn:anti/anti:anti/syn* compounds of the appropriate structure, and were determined *via* ^1H NMR analysis of the respective reaction mixtures. Products obtained by following a general procedure were performed on the scale indicated in the appropriate general procedure. Where a compound has been synthesized by a number of general procedures, the values in parenthesis relate to the yields and amounts for the specific general procedure.

4.2 Purification of Reagents

Commercial reagents were used as supplied with the following exceptions:

18-Crown-6 was recrystallised from acetonitrile, dried under vacuum and stored under nitrogen.

Benzaldehyde was distilled from calcium hydride powder under reduced pressure and stored under nitrogen in a darkened freezer.

iso-Butyraldehyde was distilled from calcium hydride powder under reduced pressure immediately before use.

Copper(II) triflate was stored in a glovebox and used immediately after being weighed out.

Bis-Copper(I) triflate toluene complex was stored in a glovebox and weighed out immediately before use.

Cyclohexane carboxaldehyde was distilled from calcium hydride powder under reduced pressure and stored under nitrogen in a darkened freezer.

Dichloromethane was distilled under nitrogen from calcium hydride powder immediately before use.

Diethyl ether was obtained from a solvent tower, where degassed diethyl ether was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diethylzinc solution was immediately transferred to a darkened Schlenk flask and stored under argon.

2-Furfural was distilled from calcium hydride powder under reduced pressure and stored under nitrogen in a darkened freezer.

ⁿHexanal was distilled from calcium hydride powder and stored under nitrogen in a darkened vessel in the freezer.

para-Methyl- β -nitrostyrene was recrystallised from diethyl ether and stored under nitrogen in a darkened freezer.

para-Methoxy- β -nitrostyrene was recrystallised from diethyl ether and stored under nitrogen in a darkened freezer.

Nitromethane was distilled under reduced pressure from calcium hydride powder and stored under nitrogen at room temperature.

β -Nitrostyrene was recrystallised from diethyl ether stored under nitrogen in a darkened freezer.

2-(2-Nitrovinyl)-furan was dissolved in diethyl ether, filtered, the solvent was removed and the yellow solid was dried under vacuum, and stored under nitrogen in a darkened freezer.

Pivaldehyde was distilled from calcium hydride powder under reduced pressure and stored under nitrogen in a darkened freezer.

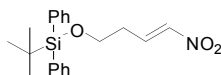
Potassium ferrous cyanide was heated at 80 °C under vacuum for 24 h and stored in a Schlenk flask.

Tetrahydrofuran was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl radical immediately before use, or obtained from a solvent tower, where degassed THF was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Toluene was obtained from a solvent tower, where degassed PhMe was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

4.3 Representative procedure for the synthesis of nitro-alkenes

tert-Butyl-((*E*)-4-nitro-but-3-enyloxy)-diphenyl-silane



To a stirred solution of 3-(*tert*-Butyl-diphenyl-silanyloxy)-propionaldehyde¹¹⁶ (789 mg, 2.52 mmol) in nitromethane (680 μ L, 12.6 mmol) at rt was added triethylamine (35 μ L, 0.25 mmol) dropwise over a 5 min period. The solution was stirred under N₂ for 16 h. Excess solvent was evaporated *in vacuo* and the crude nitro-alcohol (670 mg, 1.79 mmol) dissolved in CH₂Cl₂ (6 mL), cooled to 0 °C and MsCl (278 μ L, 3.59 mmol) added, followed by careful addition of *N,N*-diisopropylethylamine (1.10 mL, 6.28 mmol). The solution was allowed to warm to rt and stirred under N₂ until TLC analysis indicated complete consumption of the nitro-alcohol (8-16 h). Water (20 mL) and CH₂Cl₂ (20 mL) were added, and the organic phase separated, washed with HCl (2 M, 40 mL), brine (40 mL), dried (MgSO₄) and concentrated to an orange oil, which was purified by flash chromatography (silica, 20-40 % CH₂Cl₂:petrol) to give the title compound as a yellow oil (341 mg, 53 %): R_f 0.37 (30 % CH₂Cl₂: petrol); IR ν_{max} (CHCl₃) 3106 (C-H), 2932 (C-H), 2859 (C-H), 1651 (C=C), 1353 (C-O), 1095 (Si-O), 972 (HC=C) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.12 (9H, s, (CH₃)₃C), 2.48 (2H, dtd, *J* = 7.5, 6.0, 1.5, CH₂CH₂OSi), 3.83 (2H, t, *J* = 6.0, CH₂OSi), 7.05 (1H, dt, *J* = 13.5, 1.5, CH=CHNO₂), 7.31 (1H, dt, *J* = 13.5, 7.5, CH=CHNO₂), 7.41 (4H, m, ArCH), 7.46 (2H, m, ArCH), 7.66 (4H, m, ArCH); ¹³C NMR (CDCl₃, 125 MHz) δ 19.2 (C(CH₃)₃), 26.8 (C(CH₃)₃), 31.7 (CH₂CH₂OSi), 61.5 (CH₂OSi), 128.0 (ArCH), 129.9 (ArCH), 133.2 (ArC), 135.5

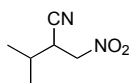
(ArCH), 139.8 (C=CHNO₂), 140.8 (CHNO₂); m/z (ESI⁺) 378 (100 %, M+Na⁺); HRMS C₂₀H₂₅NNaO₃Si calcd. 378.1495, found 378.1493.

4.4.1 General procedure A for the synthesis of β -nitronitriles

To a stirred solution of KCN (7 mg, 0.1 mmol) and 18-crown-6 (27 mg, 0.1 mmol) in MeCN (1.2 mL) was added nitroalkene (1.0 mmol) and acetone cyanohydrin (1.2 mmol, 114 μ L), the mixture was stirred at rt and monitored for consumption of nitro-alkene by TLC. The mixture was concentrated to an orange oil, which was purified by flash chromatography to afford the product.

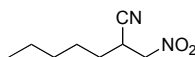
4.4.2 General procedure B for the synthesis of β -nitronitriles

To a stirred solution of KCN (7 mg, 0.1 mmol), 18-crown-6 (27 mg, 0.1 mmol) and acetone cyanohydrin (110 μ L, 1.2 mmol) in MeCN (1 mL) was added a solution of nitro-alkene (1.0 mmol) in MeCN (5 mL) *via* syringe pump over a 5 h period. After the addition was complete a further portion of acetone cyanohydrin (110 μ L, 1.2 mmol) was added and the solution stirred at rt and monitored for consumption of nitro-alkene by TLC. The mixture was concentrated to an orange oil and purified by flash chromatography to afford the product.

3-Methyl-2-nitromethylbutyronitrile - 202-a¹¹⁷

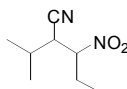
Synthesised *via* general procedure A, isolated as a colourless oil (108 mg, 73 %):

¹H NMR (CDCl₃, 400 MHz) δ 1.13 (3H, d, J = 6.8, (CH₃)₂), 1.16 (3H, d, J = 6.8, (CH₃)₂), 2.01 (1H, apt oct, J = 4.0, (CH₃)₂CH), 3.35 (1H, m, CHCN), 4.52 (1H, dd, J = 14.0, 6.0, CHHNO₂), 4.63 (1H, dd, J = 14.0, 8.4, CHHNO₂). All data was in accord with the literature.¹¹⁷

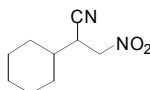
2-Nitromethyl-heptanenitrile - 202-d

Synthesised *via* general procedure B, isolated as a colourless oil (116 mg, 68 %):

R_f 0.17 (10 % acetone:petrol); IR ν_{max} (KBr disk) 2958 (C-H), 2931 (C-H), 2863 (C-H), 2248 (CN), 1561 (NO₂), 1378 (NO₂) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.92 (3H, m, CH₃), 1.35 (4H, m, CH₂), 1.47-1.75 (4H, m, CH₂), 3.40 (1H, m, CHCN), 4.51 (1H, apt ddd, J = 14.0, 7.6, 0.8, CHHNO₂), 4.64 (1H, apt ddd, J = 14.0, 7.6, 0.8, CHHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9 (CH₃), 22.3 (CH₂), 26.3 (CH₂), 29.4 (CH₂), 29.9 (CHCN), 30.9 (CH₂), 74.7 (CH₂NO₂), 118.0 (CN); m/z (EI⁺) 193 (100%, M+Na⁺); HRMS C₈H₁₄N₂NaO₂ calcd. 193.0947, found 193.0941; Anal. Calcd. for C₈H₁₄N₂O₂: C 56.45 %, H 8.29 %, N 16.46 %. Found C 56.17 %, H 8.25 %, N 16.16 %.

2-Isopropyl-3-nitro-pentanenitrile - 202-b

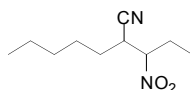
Synthesised *via* general procedure A. Isolated as a 1:1 mixture of diastereoisomers which were separable by flash chromatography (silica, 40 % CH₂Cl₂:petrol) as a white solid (123 mg, 69 %): m.p. 41-42 °C; R_f 0.26 (40 % CH₂Cl₂:petrol); IR ν_{max} (CHCl₃) 2973 (C-H), 2247 (CN), 1560 (NO₂), 1463 (C-H), 1376 (NO₂) cm⁻¹; First eluted diastereoisomer: ¹H NMR (CDCl₃, 400 MHz) δ 1.04 (3H, t, J = 7.6, CH₃CH₂), 1.12 (6H, apt t, J = 6.8 (CH₃)₂CH), 1.81 (1H m, (CH₃)₂CH), 2.02-2.25 (2H, m, CH₂CH₃), 3.21 (1H, dd, J = 10.4, 3.6, CHCN), 4.60 (1H, td, J = 10.0, 3.2, CHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 9.9 (CH₃), 19.4 (CH₃), 21.0 (CH₃), 25.6 (CH₂), 27.8 (CH), 42.4 (CHCN), 87.2 (CHNO₂), 116.5 (CN); m/z (EI⁺) 193 (100 %, M+Na⁺); HRMS C₈H₁₄N₂NaO₂ calcd. 193.0938, found 193.09475; Second eluted diastereomer: ¹H NMR (CDCl₃, 400 MHz) δ 1.04 (3H, t, J = 7.2, CH₃CH₂), 1.12-1.17 (6H, m, (CH₃)₂CH), 1.91-2.03 (2H, m, CH₂CH₃), 2.11-2.23 (1H m, (CH₃)₂CH), 2.85 (1H, apt t, J = 7.2, CHCN), 4.58-4.65 (1H, m, CHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 9.9 (CH₃), 19.4 (CH₃), 20.9 (CH₃), 25.6 (CH₂), 27.8 (CH), 42.5 (CHCN), 87.2 (CHNO₂), 116.5 (CN).

2-Cyclohexyl-3-nitro-propionitrile - 202-c

Synthesised *via* general procedure A. Isolated as a colourless oil (238 mg, 75 %): R_f 0.20 (50 % DCM:petrol); IR ν_{max} (KBr disk) 2930 (C-H), 2856 (C-H),

2245 (CN), 1558 (NO₂), 1450 (C-H), 1430 (C-H), 1377 (NO₂) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.19-1.29 (5H, m, Cy), 1.58-1.86 (6H, m, Cy), 3.34 (1H, m, CHCN), 4.55 (1H, ddd, *J* = 13.6, 6.0, 1.6, CHHNO₂) 4.64 (1H, ddd, *J* = 13.6, 6.0, 1.6, CHHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 25.2 (2 × CH₂), 25.7 (CH₂), 29.0 (CH₂), 31.0 (CH₂), 36.17 (CHCN), 37.5 (CH), 73.3 (CH₂NO₂), 117.2 (CN); *m/z* (EI⁺) 205 (39 %, M+Na⁺); HRMS C₉H₁₄N₂NaO₂ calcd. 205.0953, found 205.0930; Anal. calcd. for C₉H₁₄N₂O₂ C 59.32 %, H 7.74 %, N 15.37 %. Found C 59.45 %, H 7.84 %, N 15.34 %.

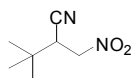
2-(1-Nitro-propyl)-heptanenitrile - 202-e



Synthesised *via* general procedure B. Isolated as a colourless oil as a 1:1 mixture of diastereomers, separable by flash chromatography (20 % Et₂O:petrol): R_f 0.23 (20 % Et₂O:petrol); IR ν_{max} (CHCl₃) 2931 (C-H), 2864 (C-H), 2248 (CN), 1561 (NO₂), 1459 (CH), 1374 (CH), 1354 (NO₂) cm⁻¹; First eluted diastereoisomer: ¹H NMR (CDCl₃, 400 MHz) δ 0.9 (3H, m, CH₃), 1.04 (3H, t, *J* = 7.2, CH₃), 1.31-1.40 (4H, m, CH₂), 1.42-1.66 (4H, m, CH₂), 2.08-2.18 (2H, m, CH₂CHNO₂), 3.22 (1H, td, *J* = 9.2, 4.0, CHCN), 4.48 (1H, td, *J* = 9.6, 4.0, CHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 9.9 (CH₃), 13.8 (CH₃), 22.2 (CH₂), 26.0 (CH₂), 26.3 (CH₂), 29.5 (CH₂), 30.9 (CH₂), 35.7 (CHCN), 89.1 (CHNO₂), 117.6 (CN); *m/z* 221 (18 %, M+Na⁺); HRMS C₁₀H₁₈N₂NaO₂ calcd. 221.12605, found 221.1258; Second diastereoisomer: ¹H NMR (CDCl₃, 400 MHz) δ 0.88-0.96 (3H, m, CH₃), 1.06 (3H, t, *J* = 7.2, CH₃), 1.37-1.47 (4H, m, CH₂), 1.41-1.54 (1H, m, CH₂), 1.54-1.69 (3H, m, CH₂), 1.98 (1H, dqd, *J* = 14.4, 7.2, 4.8, CHHCHNO₂), 2.34 (1H, ddq, *J* = 14.8, 9.6, 7.4, CHHCHNO₂), 3.04 (1H, dt, *J* = 9.6, 5.6, CHCN), 4.51 (1H, ddd, *J* = 10.0, 5.4, 5.2, CHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 10.1 (CH₃), 13.9

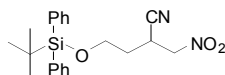
(CH₃), 22.3 (CH₂), 25.3 (CH₂), 26.7 (CH₂), 28.7 (CH₂), 31.0 (CH₂), 35.1 (CHCN), 88.4 (CHNO₂), 117.4 (CN).

3,3-Dimethyl-2-nitromethyl-butyronitrile - 202-f



Synthesised *via* general procedure A. Isolated as a white solid (172 mg, 64 %): m.p. 45-47 °C; Rf 0.43 (40 % DCM: Petrol); IR ν_{max} (CHCl₃) 2971 (C-H), 2248 (CN), 1565 (NO₂), 1374 (NO₂), 902 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.15 (9H, s, (CH₃)₃), 3.27 (1H, dd, J = 7.8, 6.8, CHCN), 4.56 (1H, d, J = 7.8, CHHNO₂), 4.58 (1H, d, J = 6.8, CHHNO₂); ¹³C NMR (CDCl₃, 100 MHz) δ 27.3 (CH₃), 33.4 (C), 41.5 (CHCN), 73.0 (CH₂NO₂), 117.7 (CN); m/z (EI⁺) 179 (100 %, M+Na⁺); HRMS C₇H₁₂N₂NaO₂ calcd. 179.0791. Found 179.0791.

4-(*tert*-Butyl-diphenyl-silanyloxy)-2-nitromethyl-butyronitrile - 202-g



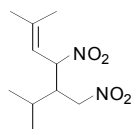
Synthesised *via* general procedure B. Isolated as a yellow oil (143 mg, 76 %); Rf 0.08 (50 % DCM:petrol); IR ν_{max} (CHCl₃) 2932 (C-H), 2860 (C-H), 2306 (CN), 1565 (NO₂), 1375 (NO₂), 1266, 1112 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.08 (9H, s, (CH₃)₃C), 1.93 (2H, m, CH₂CHCN), 3.77 (1H, m, CHCN), 3.87 (2H, m, CH₂OSi), 4.60 (1H, dd, J = 8.8, 4.4, CHHNO₂), 4.67 (1H, dd, J = 8.8, 6.0, CHHNO₂), 7.44 (6H, m, ArCH), 7.66 (4H, m, ArCH); ¹³C NMR (CDCl₃, 125 MHz) δ 19.2 (C), 26.9 (CH₃), 32.1 (CH₂), 60.0 (CH₂OSi), 74.5 (CH₂NO₂), 117.9 (CN), 127.9 (ArCH), 129.9 (ArCH), 132.6 (ArC), 135.5 (ArCH); m/z (ESI⁺) 405

(100 %, $M+Na^+$), 383 (3 %, $M+H^+$); HRMS $C_{21}H_{26}N_2NaO_3Si$ calcd. 405.1605, found 405.1617, $C_{21}H_{27}N_2O_3Si$ calcd. 383.1785, found 383.1790; Anal. calcd. for $C_{21}H_{26}N_2O_3Si$: C 65.94 %, H 6.85 %, N 7.32 %. Found C 65.67 %, H 6.81 %, N 7.14 %.

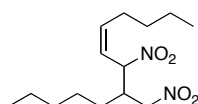
1-Methyl-2-nitro-cyclohexanecarbonitrile - 202-h



Synthesised using general procedure A. Isolated as a white crystalline solid after crystallisation from Et_2O /pentane (31 mg, 84 %): m.p. 60-62 °C; Rf 0.48 (50% DCM: petrol); IR ν_{max} ($CHCl_3$) 2949 (C-H), 2243 (CN), 1559 (NO_2), 1452, 1370 (NO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ 1.35-1.50 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.8 (2H, m, CH_2), 2.02 (1H, m, CHH), 2.18 (1H, m, CHH), 2.24 (1H, dd, $J = 10.0, 3.2$, $CHHCHNO_2$), 2.28-2.33 (1H, m, CHH), 4.21 (1H, dd, $J = 9.6, 3.2$, $CHNO_2$); ^{13}C ($CDCl_3$, 125 MHz) δ 20.5 (CH_2), 23.9 (CH_2), 24.1 (CH_3), 29.0 (CH_2), 37.8 (CH_2), 38.4 (C), 90.5 ($CHNO_2$), 119.7 (CN); m/z (EI^+) 191 (100 %, $M+Na^+$); HRMS $C_8H_{12}N_2NaO_2$ calcd. 191.1868, found 191.0798; Anal calcd. For $C_8H_{12}N_2O_2$ C 57.13 %, H 7.19 %, N 16.66 %. Found C 57.06 %, H 7.17 %, N 16.48 %.

2,6-Dimethyl-4-nitro-5-nitromethyl-hept-2-ene

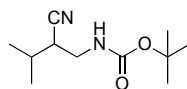
Isolated as a by-product during synthesis of 3-methyl-2-nitromethylbutyronitrile as a colourless oil: IR ν_{\max} (thin film) 2966 (C-H), 2941 (C-H), 2878 (C-H), 1668, 1567, 1546, 1428, 1344 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.93 (3H, d, $J = 7.2$, $(\text{CH}_3)(\text{CH}_3)\text{CH}$), 1.05 (3H, d, $J = 7.2$, $(\text{CH}_3)(\text{CH}_3)\text{CH}$), 1.79 (3H, d, $J = 0.8$, $(\text{CH}_3)(\text{CH}_3)\text{C}=\text{C}$), 1.83 (3H, d, $J = 1.2$, $(\text{CH}_3)(\text{CH}_3)\text{C}=\text{C}$), 1.84 (1H, septd, $J = 7.2$, 4.2, $(\text{CH}_3)_2\text{CH}$), 3.09 (1H, m, CHCH_2NO_2), 4.26 (1H, dd, $J = 14.4$, 6.4, CHHNO_2), 4.38 (1H, dd, $J = 14.0$, 4.8, CHHNO_2), 5.30 (1H, dsept, $J = 10.0$, 1.2, $\text{HC}=\text{C}(\text{CH}_3)_2$), 5.34 (1H, apt q, $J = 10.0$, CHNO_2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 16.9 ($(\text{CH}_3)_2\text{CH}$), 18.6 ($(\text{CH}_3)_2\text{C}=\text{C}$), 20.3 ($(\text{CH}_3)_2\text{CH}$), 25.8 ($(\text{CH}_3)_2\text{CH}$), 27.7 ($(\text{CH}_3)_2\text{C}=\text{C}$), 29.7 ($(\text{CH}_3)_2\text{CH}$), 45.7 (CHCH_2NO_2), 72.6 (CH_2NO_2), 86.1 (CHNO_2), 117.1 ($\text{CH}=\text{C}(\text{CH}_3)_2$), 145.0 ($\text{CH}=\text{C}(\text{CH}_3)_2$); m/z (EI^+) 253 (62%, $\text{M}+\text{Na}^+$); HRMS $\text{C}_{10}\text{H}_{18}\text{N}_2\text{NaO}_4$ calcd. 253.11588. Found 253.1151.

(Z)-7-Nitro-8-nitromethyl-tridec-5-ene - 205

Isolated as a by product during the synthesis of 2-nitromethyl-heptanenitrile under the conditions described in general procedure A as a colourless oil (71 mg, 23 %): R_f 0.28 (40 % DCM:petrol); IR ν_{\max} (CHCl_3) 3696, 2931 (C-H), 2862 (C-H), 1601 (C=C), 1557 (NO_2), 1458, 1380 (NO_2), 908 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 0.89 (3H, t, $J = 7.0$, CH_3), 0.92 (3H, t, $J = 7.5$, CH_3), 1.20-1.50 (12H, m,

CH_2), 2.20 (2H, m, $\text{CH}_2\text{CH}=\text{CH}$), 2.83 (1H, m, CHCH_2NO_2), 4.43 (1H, dd, $J = 13.7, 5.2$, CHHNO_2), 4.57 (1H, dd, $J = 13.7, 5.6$, CHHNO_2), 5.49 (1H, dd, $J = 9.9, 8.8$, CHNO_2), 5.57 (1H, apt tt, $J = 10.4, 1.0$, $\text{CH}=\text{CHCH}_2$), 5.96 (1H, dt, $J = 10.4, 7.8$, $\text{CH}=\text{CHCH}_2$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.9 ($2\times\text{CH}_3$), 22.3 (CH_2), 26.0 (CH_2), 27.7 (CH_2), 28.0 (CH_2), 31.2 (CH_2), 31.3 (CH_2), 31.4 (CH_2), 40.9 (CHCH_2NO_2), 74.5 (CH_2NO_2), 85.5 (CHNO_2), 120.8 ($\text{CH}=\text{CHCH}_2$), 141.6 ($\text{CH}=\text{CHCH}_2$); m/z (EI^+) 309 (100%, $\text{M}+\text{Na}^+$), 304 (3 %, $\text{M}+\text{NH}_4^+$); HRMS $\text{C}_{14}\text{H}_{26}\text{N}_2\text{NaO}_4$ calcd. 309.1785. Found 309.1774. $\text{C}_{14}\text{H}_{30}\text{N}_3\text{O}_4$ calcd. 304.2231. Found 304.2236.

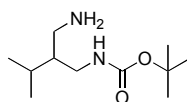
(2-Cyano-3-methyl-butyl)-carbamic acid *tert*-butyl ester - 208



To a stirred solution of 3-methyl-2-nitromethylbutyronitrile **202-a** (0.30 g, 2.1 mmol) in EtOH (40 mL) was added zinc powder (2.07 g, 31.7 mmol) and 6 M $\text{HCl}_{(\text{aq})}$ (10 mL) and the reaction was stirred for 2 h. Excess zinc was removed by filtration, the EtOH removed *in vacuo* and NaOH (1 M) added until pH 10. The aqueous layer was extracted into CH_2Cl_2 (3×20 mL), the combined organic layers washed with brine (20 mL), dried (MgSO_4), and evaporated to dryness. The crude amino-nitrile (0.26 g, 2.4 mmol) was dissolved in CH_2Cl_2 (12 mL), Boc anhydride (0.57 mg, 2.6 mmol) was added and the solution stirred at rt for 12 h. Excess solvent was removed *in vacuo* and the resultant product purified by flash chromatography (silica, 20 % Et_2O :petrol) to yield the title compound (352 mg, 79 %) as a white solid: m.p. 54-55 °C; R_f 0.37 (30 % CH_2Cl_2 :petrol); IR ν_{max} (CHCl_3) 3456 (NH), 2970 (C-H), 2241 (CN), 1713 (C=O), 1368 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.07 (3H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)(\text{CH}_3)$), 1.09 (3H, d, $J = 6.8$,

CH(CH₃)(CH₃)), 1.43 (9H, s, C(CH₃)₃), 1.90 (1H, apt oct, $J = 6.8$, CH(CH₃)₂), 2.78 (1H, ddd, $J = 9.6, 5.2, 5.2$, CHCN), 3.18 (1H, ddd, $J = 14.0, 9.6, 5.2$, CHHNH), 3.47 (1H, ddd, $J = 13.6, 5.2, 5.2$, CHHNH), 5.05 (1H, brs, NH); ¹³C NMR (CDCl₃, 100 MHz) δ 18.7 (CH₃), 20.9 (CH₃), 28.1 (CH), 28.7 (CH₃), 40.3 (CHCN), 41.7 (CH₂NH), 80.1 (C(CH₃)₃), 120.1 (CN), 155.7 (C=O); m/z (ESI) 235 (M+Na⁺); HRMS C₁₁H₂₀N₂NaO₂ calcd. 235.1417. Found 235.1423; Anal. Calcd. For C₁₁H₂₀N₂O₂ C 62.24 %, H 9.50 %, N 13.20 %. Found C 62.27 %, H 9.62 %, N 13.16 %.

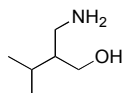
(2-Aminomethyl-3-methyl-butyl)-carbamic acid *tert*-butyl ester - 209



To a stirred solution of **208** (75 mg, 0.35 mmol) in Et₂O (2 mL) was added LiAlH₄ (50 mg, 1.41 mmol) and heated at reflux for 4 h. The reaction was cooled to 0 °C, and water (0.5 mL), 20 % NaOH_(aq) (0.5 mL) and water (1.5 mL) were added dropwise and sequentially. The granular precipitate was filtered through cotton wool, water (15 mL) and Et₂O (15 mL) added to the filtrate, the layers separated and the aqueous layer extracted with Et₂O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo* to yield the title compound as a yellow oil (68 mg, 89 %): R_f 0.12 (2 % MeOH:1 % NEt₃:CH₂Cl₂); IR ν_{\max} (CHCl₃) 3455 (NH), 3387 (NH), 2875 (C-H), 1713 (C=O), 1391, 1366 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.89 (3H, d, $J = 7.0$, CH(CH₃)(CH₃)), 0.91 (3H, d, $J = 7.0$, CH(CH₃)(CH₃)), 1.28 (1H, m, CHCH₂NH₂), 1.54 (2H, brs, NH₂), 1.69 (1H, apt oct, $J = 6.8$, CH(CH₃)₂), 2.63 (1H, dd, $J = 12.5, 7.5$, CHHNH₂), 2.82 (1H, dd, $J = 12.5, 4.0$, CHHNH₂), 3.09 (1H, ddd, $J = 13.0, 7.5, 5.5$, CHHNHBoc), 3.29 (1H, ddd, $J = 13.0, 5.5, 5.5$, CHHNHBoc), 5.05 (1H, brs, NHBoc); ¹³C NMR (CDCl₃, 100 MHz) δ 19.7

(CH₃), 20.1 (CH₃), 27.8 (CH), 28.5 (CH₃), 41.3 (CH₂), 42.6 (CH₂), 47.1 (CH), 78.9 (C), 156.3 (CO); m/z 239 (16.6 %, M+Na⁺); HRMS C₁₁H₂₄N₂NaO₂ calcd. 239.1730. Found 239.1724.

2-Aminomethyl-3-methyl-butan-1-ol - **211**¹¹⁸

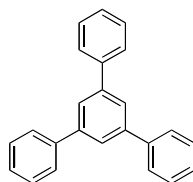


To a stirred solution of 3-methyl-2-nitromethylbutyronitrile **202-a** (5.41g, 38.1 mmol) in THF (165 mL) at 0 °C was added a solution of TiCl₃ (20 % by weight in HCl_(aq), 84 mL, 152.2 mmol). After 1 h the reaction was allowed to warm to rt and stirred until the purple colour disappeared (3-4 days). The reaction was extracted with Et₂O (3 × 40 mL), and the combined extracts washed with brine (50 mL), dried (MgSO₄) and solvent removed *in vacuo* to afford the crude and unstable α-cyano aldehyde **210** as a yellow oil (3.43 g): ¹H NMR (CDCl₃, 500 MHz) δ 1.16 (3H, d, *J* = 3.5, (CH₃)₂), 1.24 (3H, d, *J* = 3.5, (CH₃)₂), 2.52 (1H, m, CH(CH₃)₂), 3.41 (1H, dd, *J* = 5.0, 0.8, CHCN), 9.58 (1H, d, *J* = 0.8, O=CH); ¹³C NMR (CDCl₃, 125 MHz) δ 19.7 (CH₃), 21.3 (CH₃), 27.8 (CH), 51.9 (CH), 114.8 (CN), 191.9 (CO).

The yellow oil (3.43 g, 38.1 mmol) was immediately dissolved in Et₂O (200 mL), cooled to 0 °C and LiAlH₄ (8.68 g, 228.6 mmol) added portion-wise over 10 min. The mixture was heated at reflux for 4 h. The mixture was cooled to 0 °C and water (8.6 mL), 20 % NaOH_(aq) (8.6 mL) and water (25.8 mL) were added dropwise and sequentially. After a granular precipitate had formed the solution was filtered through cotton wool, water (20 mL) and Et₂O (50 mL) added to the filtrate, the layers separated and the aqueous layer extracted with Et₂O (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and concentrated *in vacuo*. The resulting oil was purified by ion

exchange chromatography (SCX Strata™, 2M NH₃ in MeOH) to yield the title compound as a yellow oil (2.71 g, 77 %), which was further purified by bulb-to-bulb distillation to give a colourless oil (2.25 g, 64% over 2 steps). ¹H NMR (CDCl₃, 500 MHz) δ 0.86 (3H, d, *J* = 1.4, CH(CH₃)(CH₃)), 0.88 (3H, d, *J* = 1.4, CH(CH₃)(CH₃)), 1.39 (1H, m, CHⁱpr), 1.63 (1H, apt oct, *J* = 6.5, CH(CH₃)₂), 2.79 (1H, dd, *J* = 12.2, 9.2, CHHOH), 2.84 (2H, brs, NH₂), 3.04 (1H, ddd, *J* = 12.1, 3.3, 1.6, CHHOH), 3.70 (1H, dd, *J* = 10.6, 8.3, CHHNH₂), 3.78 (1H, ddd, *J* = 10.6, 3.3, 1.5, CHHNH₂). All other data was in accord with the literature.¹¹⁸

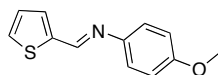
1,3,5-Triphenylbenzene - 214¹¹⁹



To a solution of β-nitro styrene (149 mg, 1.0 mmol) in DMF (1 mL) in a sealed tube was added Na₂CO₃ (106 g, 1.0 mmol) and K₄[Fe(CN)₆] (132 g, 0.4 mmol). The reaction was heated at 120 °C for 16 h (conventional heating) or 120 °C for 1 h (microwave heating), then allowed to cool to rt. The reaction was quenched by the addition of HCl (2.0 M, 15 mL) and extracted with Et₂O (3 × 20 mL). The organic layers were combined and washed with brine (3 × 20 mL), dried (MgSO₄) and the solvent removed *in vacuo* to provide an orange oil, which was purified by flash chromatography (silica, 20 % Et₂O: petrol) to afford the title compound as an orange crystalline solid (86 mg, 84 %): m.p. 170-172 °C, lit¹¹⁹ 174-175 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.39-7.43 (3H, m, HAr), 7.52 (6H, t, *J* = 7.6, HAr), 7.74 (6H, m, HAr), 7.83 (3H, s, HAr). All other data was in accord with the literature.¹¹⁹

4.5 Representative procedure for the synthesis of aldimines

(4-Methoxy-phenyl)-[1-thiophen-2-yl-meth-(E)-ylidene]-amine



Alumina (160 g) was added to a solution of *para*-anisidine (20.0 g, 162 mmol) and 2-thiophene carboxaldehyde (16.5 mL, 162 mmol) in DCM (500 mL), and the mixture stirred at rt for 16 h. The reaction mixture was filtered through celite, washed with EtOAc and concentrated *en vacuo*. The brown solid was purified by crystallisation from EtOAc/hexane to yield the title compound as yellow crystals (31.3 g, 89 %): m.p. 168-171 °C; IR ν_{max} 3070 (C-H), 2834 (C-OAr), 1614 (C=N), 1500 (C=N), 1244, 832 (C-H) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 3.81 (3H, s, OMe), 6.91 (2H, m, HAr), 7.11 (1H, dd, $J = 5.0, 3.5$, HAr), 7.23 (2H, m, HAr), 7.44 (1H, m, HAr), 7.46 (1H, m, HAr), 8.57 (1H, s, HC=N); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.6 (OMe), 114.5 (HAr $\times 2$), 122.4 (HAr $\times 2$), 127.8 (HAr), 129.9 (HAr), 131.7 (HAr), 143.2 (Ar), 144.4 (Ar), 151.2 (Ar), 158.4 (C=N); m/z (ESI^+) 218 ($[\text{M}+\text{H}]^+$, 100 %); HRMS $\text{C}_{12}\text{H}_{12}\text{NOS}$ calc. 218.0640, found 218.0640; Anal. calcd. for $\text{C}_{12}\text{H}_{12}\text{NOS}$ C 66.33 %, H 5.10 %, N 6.45 %, found C 66.40 %, H 5.12 %, N 6.42 %.

4.6.1 General procedure C for the synthesis of β -nitrotrifluoroacetamides

Copper (II) triflate (0.03 mmol, 12 mg) was placed in a 50 mL flame dried round bottomed flask. THF (7 mL) was added, and the reaction vessel cooled to -78

°C. Diethylzinc or dimethylzinc solution (0.74 mL, 1 M soln. in hexanes) was added, and the solution allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 5 min. A solution of nitroalkene (0.67 mmol) in THF (2 mL) was added *via* cannular, and the reaction warmed to rt. The reaction was allowed to stir at rt for 2 h (forming a dark brown solution), then cooled to $-78\text{ }^{\circ}\text{C}$, a solution of imine (1.34 mmol) in THF (1 mL) was added *via* syringe, followed by a 1:1 mixture of TFA:THF (2.35 mmol, 0.17 mL). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then removed from the ice bath, quenching after 5 min with sat. NaHCO_3 soln. The aqueous layer was extracted into Et_2O ($3 \times 20\text{ mL}$), the combined organics washed with brine (20 mL), dried (MgSO_4), solvent evaporated, and a small sample taken for crude NMR analysis. The resulting yellow oil was dissolved in DCM (10 mL), cooled in a dry-ice/acetone bath and DIPEA (1.48 mmol, 0.25 mL) and TFAA (1.48 mmol, 0.20 mL) added. The reaction was warmed to rt and stirred for 30 min. After this time the organic solution was washed with 2 M HCl ($2 \times 15\text{ mL}$), water (15 mL) dried (MgSO_4) and the solvent removed. The yellow oil was purified by flash column chromatography to give the desired product.

4.6.2 General procedure D for the synthesis of β -nitrotrifluoroacetamides

To a stirred mixture of nitroalkene (1.00 mmol), copper complex **223** (0.05 mmol) and pivalamide (0.80 mmol) in Et_2O (5 mL) at $-70\text{ }^{\circ}\text{C}$ was added Et_2Zn (1.1 mmol, 1 M in hexanes) dropwise. The mixture was stirred at this temperature until the reaction was complete by tlc analysis (approx. 20 h). The solvent was removed under high vacuum at rt, replaced with THF (8 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. A solution of imine (2.00 mmol) in THF (1 mL) was added and stirred for 5 min. A solution of TFA (3.5 mmol) in THF (1 mL) was then added dropwise and the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then removed from the cold bath and stirred for 5 min, then quenched with saturated aq. NaHCO_3 (15

mL). The layers were separated and the aqueous phase extracted with Et₂O (15 mL), then the combined organics washed with sat. NaHCO₃ (2 × 15 mL), brine (15 mL) dried (MgSO₄) and solvent removed *in vacuo* to provide the crude β -nitroamine. A small sample was removed for diastereoselectivity calculation (comparison of the ¹H NMR signal of the CHNO₂ protons). The remainder of the crude β -nitroamine was immediately dissolved in DCM (10 mL), cooled to –78 °C and DIPEA (2.2 mmol) and (TFA)₂O added. The reaction was warmed to rt and stirred for 1 h before the addition of 2 M HCl (10 mL). The organic layer was washed with 2 M HCl (3 × 10 mL), dried (MgSO₄) and solvent removed. The crude β -nitrotrifluoroacetamide was then purified by column chromatography to yield the products.

4.6.3 General procedure E for the synthesis of β -nitrotrifluoroacetamides

Ligand **229** (0.02 mmol) and (CuOTf)₂.PhMe (0.01 mmol) were added to a flame dried flask in a glove box, and the flask equipped with a septum. The flask was removed from the glove box and dry PhMe (2 mL) added. The suspension was stirred at rt for 10 min to provide a yellow solution. The solution was cooled to –30 °C and stirred for 10 min. ZnEt₂ (1.10 mmol, 1 M in hexanes) was added dropwise and stirred for 10 min. to provide an orange solution. A solution of nitroalkene (1.00 mmol) in PhMe (2 mL) was added over 5 min and stirred for 20 min before warming to rt. The reaction was stirred at rt until complete by tlc analysis (approx 16 h). The solvent was removed under high vacuum at 30 °C and replaced with THF (8 mL) and cooled to –78 °C. A solution of imine (2.00 mmol) in THF (1 mL) was added and stirred for 5 min. A solution of TFA (3.50 mmol) in THF (1 mL) was then added dropwise and the reaction stirred at –78 °C for one hour, then removed from the cold bath and stirred for 5 min then

quenched with saturated aq. NaHCO_3 (15 mL). The layers were separated and the aqueous phase extracted with Et_2O (15 mL), then the combined organics washed with sat. NaHCO_3 (2×15 mL), brine (15 mL) dried (MgSO_4) and solvent removed *in vacuo* to provide crude β -nitroamine. A small sample was removed for diastereoselectivity calculation (comparison of the ^1H NMR signal of the CHNO_2 protons). The remainder of the crude β -nitroamine was immediately dissolved in DCM (10 mL), cooled to -78°C and DIPEA (2.20 mmol) and $(\text{TFA})_2\text{O}$ added (2.20 mmol). The reaction was warmed to rt and stirred for 1 h before the addition of 2 M HCl (10 mL). The organic layer was washed with 2 M HCl (3×10 mL), dried (MgSO_4) and solvent removed. The crude β -nitrotrifluoroacetamide was then purified by column chromatography to yield the products.

4.6.4 General procedure F for the synthesis of β -nitroamines

To a stirred mixture of nitroalkene (1.00 mmol) and $\text{Cu}(\text{OTf})_2$ (0.05 mmol) in dry Et_2O (3 mL) at -78°C was added Et_2Zn (1.10 mmol, 1M in hexane). The resulting orange solution was stirred at this temperature for 10 min before being warmed to rt. Once the nitroalkene was consumed by tlc analysis (approx. 90 min), the brown suspension was cooled to -78°C . A solution of imine (2.00 mmol) in dry Et_2O (2 mL) was added and the mixture stirred for 20 min. A solution of TFA (3.50 mmol) in Et_2O (0.6 mL) was added dropwise over 20 seconds and the reaction stirred for 2 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid and vivid yellow supernatant. The reaction was quenched by the addition of Et_2O (5 mL) and saturated aq. NaHCO_3 (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (2×5 mL). The organic layers were combined and the

solvent removed *in vacuo* to provide crude β -nitroamine. Note: MgSO_4 was not used to dry the product β -nitroamines prior to solvent removal because the products were found to be mildly unstable towards this reagent. The crude mixture was purified by flash chromatography (due to the instability of these compounds the chromatography must be through a short (~6 cm) column and performed with haste) to yield the product.

4.6.5 General procedure G for the synthesis of β -nitroamines

Ligand **229** (0.02 mmol) and $(\text{CuOTf})_2\cdot\text{PhMe}$ (0.01 mmol) were added to a flame dried flask in a glove box, and the flask equipped with a septum. The flask was removed from the glove box and dry PhMe (2 mL) added. The suspension was stirred at rt for 10 min to provide a yellow solution. The solution was cooled to $-30\text{ }^\circ\text{C}$ and stirred for 10 min. A solution of ZnEt_2 (1.10 mmol, 1 M in hexanes) was added dropwise and stirred for 10 min. to provide an orange solution. A solution of nitroalkene (1.00 mmol) in PhMe (2 mL) was added over 5 min and stirred for 20 min before warming to rt. The reaction was stirred at rt until complete by tlc analysis (approx 16 h), and then cooled to $-78\text{ }^\circ\text{C}$. A solution of imine (2.0 mmol) in dry Et_2O (2 mL) was added and the mixture stirred for 20 min. A solution of TFA (3.5 mmol) in Et_2O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 2 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid and vivid yellow supernatant. The reaction was quenched by the addition of Et_2O (5 mL) and saturated NaHCO_3 soln. (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The organic layers were combined and the solvent removed *in vacuo* to provide crude β -nitroamine. Note: MgSO_4 was not used to dry the product β -nitroamines prior to solvent removal because the

products were found to be mildly unstable towards this reagent. The crude mixture was purified by flash chromatography (due to the instability of these compounds the chromatography must be through a short (~6 cm) column and performed with haste) to yield the product.

4.6.6 General procedure H for the synthesis of β -nitroamines

Ligand **229** (0.04 mmol) and $(\text{CuOTf})_2 \cdot \text{PhMe}$ (0.02 mmol) were added to a flame dried flask in a glove box, and the flask equipped with a septum. The flask was removed from the glove box and dry PhMe (2 mL) added. The suspension was stirred at rt for 10 min to provide a yellow solution. The solution was cooled to $-30\text{ }^\circ\text{C}$ and stirred for 10 min. A solution of ZnEt_2 (2.20 mmol, 1 M in hexanes) was added dropwise and stirred for 10 min. to provide an orange solution. A solution of nitroalkene (2.00 mmol) in PhMe (2 mL) was added over 5 min and stirred for 20 min before warming to rt. The reaction was stirred at rt until complete by tlc analysis (approx 16 h), and then cooled to $-78\text{ }^\circ\text{C}$. A solution of imine (1.00 mmol) in dry Et_2O (2 mL) was added and the mixture stirred for 20 min. A solution of TFA (2.5 mmol) in Et_2O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 2 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid and vivid yellow supernatant. The reaction was quenched by the addition of Et_2O (5 mL) and saturated NaHCO_3 soln. (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The organic layers were combined and the solvent removed *in vacuo* to provide crude β -nitroamine. Note: MgSO_4 was not used to dry the product β -nitroamines prior to solvent removal because the products were found to be mildly unstable towards this reagent. The crude mixture was purified by flash chromatography (due to the instability of these

compounds the chromatography must be through a short (~6 cm) column and performed with haste) to yield the product.

4.6.7 General procedure 1 for the synthesis of β -nitrotrifluoroacetamides

Ph_2Zn (294 mg, 1.34 mmol) was placed in a flame dried round bottom flask in a glovebox. The flask was removed from the glovebox and copper (II) triflate (12 mg, 0.03 mmol) added. THF (7 mL) was added, and the reaction vessel cooled to $-78\text{ }^\circ\text{C}$ and allowed to stir at $-78\text{ }^\circ\text{C}$ for five min. A solution of nitro-alkene (0.670 mmol) in THF (2 mL) was added *via* cannular, and the reaction warmed to rt. The reaction was allowed to stir at rt for 48 hrs (forming a dark brown solution), then cooled to $-78\text{ }^\circ\text{C}$, a solution of imine (1.341 mmol) in THF (1 mL) was added *via* syringe, followed by a 1:1 mixture of TFA:THF (2.347 mmol, 1.74 mL). The reaction was stirred at $-78\text{ }^\circ\text{C}$ for one hr, then removed from the $-78\text{ }^\circ\text{C}$ bath, quenching after five min with sat. NaHCO_3 soln. The aqueous layer was extracted into diethyl ether ($3 \times 20\text{ mL}$), the combined organics washed with brine (20 mL), dried (MgSO_4), solvent evaporated, and a small sample taken for crude NMR analysis. The resulting yellow oil was dissolved in DCM (10 mL), cooled in an ice bath and DIPEA (1.475 mmol, 0.25 mL) and TFAA (1.475 mmol, 0.20 mL) added. The reaction was warmed to rt and stirred for 30 min. After this time the organic solution was washed with 2 M HCl ($2 \times 15\text{ mL}$), water (15 mL) dried (MgSO_4) and solvent removed. The yellow oil was purified by flash chromatography to give the desired product.

4.6.8 General procedure J for the synthesis of β -nitroamines

Ph₂Zn (294 mg, 1.34 mmol) was placed in a flame dried round bottom flask in a glovebox. The flask was removed from the glovebox and copper (II) triflate (12 mg, 0.03 mmol) added. Toluene (7 mL) was added, and the reaction vessel cooled to $-78\text{ }^{\circ}\text{C}$ and allowed to stir at $-78\text{ }^{\circ}\text{C}$ for five min. A solution of nitro-alkene (0.670 mmol) in toluene (2 mL) was added *via* cannular, and the reaction warmed to rt. The reaction was allowed to stir at rt for 48 h (forming a dark brown solution). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, a solution of imine (1.341 mmol) in Et₂O (1 mL) was added *via* syringe, followed by a 1:1 mixture of TFA:Et₂O (2.347 mmol, 1.74 mL). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for two h, then removed from the $-78\text{ }^{\circ}\text{C}$ bath, quenching after one h with sat. NaHCO₃ soln. The aqueous layer was extracted into diethyl ether (3 \times 20 mL), the combined organics washed with brine (20 mL), dried (MgSO₄), solvent evaporated and the resultant oil purified by flash chromatography to give the desired product.

4.6.9 General procedure K for the synthesis of β -nitroamines

Copper (II) triflate (0.034 mmol, 12 mg) was placed in a 50 mL flame dried round bottomed flask. THF (7 mL) was added, and the reaction vessel cooled to $-78\text{ }^{\circ}\text{C}$. A solution of ZnEt₂ (0.74 mL, 1 M soln. in hexanes) added, and the solution allowed to stir at $-78\text{ }^{\circ}\text{C}$ for five min. A solution of nitro-alkene (0.670 mmol) in THF (2 mL) was added *via* cannular, and the reaction warmed to rt. The reaction was allowed to stir at rt for 48 h (forming a dark brown solution). The solvent was then removed under vacuum and Et₂O (5 mL) added.

The solution was then cooled to $-78\text{ }^{\circ}\text{C}$, a solution of imine (1.341 mmol) in Et_2O (1 mL) was added *via* syringe, followed by a 1:1 mixture of TFA: Et_2O (2.347 mmol, 1.74 mL). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for two h, then removed from the ice bath, quenching after one h with sat. NaHCO_3 soln. The aqueous layer was extracted into diethyl ether ($3 \times 20\text{ mL}$), the combined organics washed with brine (20 mL), solvent evaporated and the resulting yellow oil purified by flash chromatography to give the desired product.

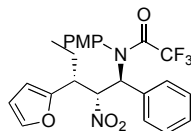
4.6.10 General procedure L for the degradation of *syn/anti*- β -nitroamines

To a solution of *syn/anti*- β -nitroamine (5 mg) in CDCl_3 was added TFA (1 drop), and the solution allowed to stand until complete degradation was observed by ^1H NMR ($\sim 1\text{ h}$). The solvent was removed *en vacuo*, and the oily residue passed through a short silica plug to yield the parent nitroalkane, which was analysed for *ee* by HPLC.

4.6.11 General procedure M for the degradation of *syn/anti*- β -nitrotrifluoroacetamides.

To a solution of *syn/anti*- β -nitrotrifluoroacetamide (50 mg) in IPA/water (10:1, 5 mL) was added NaBH_4 (10 eq), and the reaction was stirred at rt for 5 h. The IPA was removed *en vacuo* and water (5 mL) and DCM (10 mL) added. The layers were separated, the aqueous layer extracted into DCM ($2 \times 10\text{ mL}$), the combined organics dried (MgSO_4) and the oily residue passed through a short silica plug to yield the parent nitroalkane, which was analysed for *ee* by HPLC.

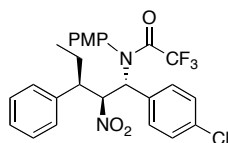
2,2,2-Trifluoro-*N*-((1*S*,2*R*,3*R*)-3-furan-2-yl-2-nitro-1-phenyl-pentyl)-*N*-(4-methoxy-phenyl)-acetamide - 231-5



Synthesised *via* general procedures C (221 mg, 69 %) and E (236 mg, 74 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 90:10:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as a red crystalline solid: m.p. 121-123 °C; R_f 0.23 (10 % EtOAc:petrol); [α]_D²² + 32.34 (c 0.76, CHCl₃); IR ν_{max} 3011 (C-H), 2972 (C-H), 2841 (C-H), 1698 (C=O), 1556 (NO₂), 1512, 1255 (CF), 1183 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.97 (3H, t, *J* = 7.3, CH₃CH₂), 1.64 (1H, ddq, *J* = 14.1, 11.7, 7.2, CHHCH₃), 2.23 (1H, dqd, *J* = 13.7, 7.4, 2.6, CHHCH₃), 3.42 (1H, apt dt, *J* = 11.6, 3.2, CHCH₂CH₃), 3.81 (3H, s, OMe), 5.51 (1H, dd, *J* = 11.4, 3.8, CHNO₂), 5.98 (1H, dd, *J* = 8.8, 1.9, HAr), 6.22 (1H, d, *J* = 3.3, HAr), 6.38 (1H, dd, *J* = 3.3, 1.9, HAr), 6.53 (1H, dd, *J* = 8.8, 2.9, HAr), 6.56 (1H, d, *J* = 11.7, CHNTFA), 6.94 (3H, m, HAr), 1.17-1.30 (4H, m, HAr); ¹³C NMR (CDCl₃, 100 MHz) δ 12.5 (CH₃), 21.2 (CH₂CH₃), 41.9 (CHCH₂CH₃), 55.5 (OMe), 60.0 (CHNTFA), 88.8 (CHNO₂), 108.2 (HAr), 110.7 (HAr), 113.8 (HAr), 113.8 (HAr), 115.7 (q, *J* = 287.5, CF₃), 126.5 (Ar), 128.6 (HAr), 128.8 (HAr), 129.0 (HAr), 129.4 (HAr), 130.5 (HAr), 130.5 (HAr), 133.0 (HAr), 133.4 (Ar), 142.3 (HAr), 152.0 (Ar), 158.2 (q, *J* = 35.9, C=O), 160.3 (Ar); ¹⁹F (CDCl₃, 376 MHz) δ -66.9 (3F, s, CF₃); m/z (ESI⁺) 499 (M+Na⁺, 100 %), 494 (M+NH₄⁺, 38 %), 477 (M+H⁺, 11 %); HRMS C₂₄H₂₃F₃N₂NaO₅ calcd. 499.1451, found 499.1438, C₂₄H₂₇F₃N₃O₅ calcd. 494.1897, found 494.1883, C₂₄H₂₄F₃N₂O₅ calcd. 477.1632, found 477.1635; Anal. calcd. for C₂₄H₂₃F₃N₂O₅ C 60.50 %, H 4.87 %, N 10.12 %, F 12.51 %, O 11.99 %.

N 5.88 %. Found C 60.75 %, H 4.90 %, N 5.66 %; HPLC (Chiracel OD-H 250 mm column with guard 99.5:0.5 hexane:IPA, 0.5 mL min⁻¹), 19.5 (major), 22.2 (minor) shows 89 % *ee*.

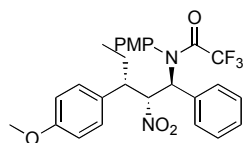
***N*-[(1*R*,2*S*,3*R*)-1-(4-Chloro-phenyl)-2-nitro-3-phenyl-pentyl]-2,2,2-trifluoro-*N*-(4-methoxy-phenyl)-acetamide - 225-2**



Synthesised *via* general procedures C (211 mg, 60 %) and D (206 mg, 59 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 55:15:30:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 65:0:35:0. Isolated as a 80:0:20:0 mixture of diastereoisomers as a yellow oil: *R*_f 0.29 (10 % EtOAc:petrol); [α]_D²² – 2.5 (c 0.83, CHCl₃); IR ν_{max} 3011 (C-H), 2967 (C-H), 2878 (C-H), 1698 (C=O), 1606, 1555 (NO₂), 1511, 1256 (CF), 1182 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.78 (3H, t, *J* = 7.3, CH₃CH₂), 1.75 (1H, m, CHHCH₃), 2.07 (1H, m, CHHCH₃), 3.15 (1H, ddd, *J* = 14.7, 5.3, 3.0, CHCH₂CH₃), 3.78 (3H, s, OMe), 5.66 (1H, dd, *J* = 10.2, 5.4, CHNO₂), 6.06 (1H, d, *J* = 10.1, CHNTFA), 6.22 (1H, d, *J* = 7.9, HAr), 6.61 (1H, dd, *J* = 8.8, 2.7, HAr), 6.79-6.90 (3H, m, HAr), 7.17 (4H, m, HAr), 7.37 (4H, m, HAr); Minor diastereoisomer - 0.53 (3H, t, *J* = 7.3, CH₃CH₂), 2.06 (1H, m, CHHCH₃), 3.30 (1H, m, CHCH₂CH₃), 3.81 (3H, s, OMe), 6.02 (1H, d, *J* = 9.1, CHNTFA), 6.66 (1H, m, HAr), remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 100 MHz) δ 12.0 (CH₃CH₃), 23.3 (CH₂CH₃), 48.1 (CHCH₂CH₃), 55.5 (OMe), 62.9 (CHNTFA) 91.4 (CHNO₂), 113.8 (HAr), 114.0 (HAr), 116.1 (q, *J* = 290.4, CF₃), 127.1 (Ar), 127.5 (HAr), 127.9 (HAr), 128.2 (HAr), 128.3 (HAr), 128.5

(HAr), 128.8 (HAr), 129.1 (HAr), 129.3 (HAr), 130.1 (HAr), 130.5 (HAr), 131.3 (HAr), 131.5 (Ar), 135.6 (Ar), 138.6 (Ar), 158.4 (q, $J = 36.0$, C=O), 160.4 (Ar); Minor diastereoisomer - 26.3 (CH₂CH₃), 90.6 (CHNO₂) remaining peaks could not be distinguished; ¹⁹F NMR (CDCl₃, 376 MHz) δ -67.1 (3F, s, CF₃); m/z (ESI⁺) 543 (M+Na⁺, 100 %), 538 (M+NH₄⁺, 61 %); HRMS C₂₆H₂₄ClF₃N₂NaO₄ calcd. 543.1269, found 543.1263, C₂₆H₂₈ClF₃N₃O₄ calcd. 538.1715, found 538.1699; HPLC measured for the parent nitro-alkane obtained *via* general procedure L, (Chiracel OD-H 150 mm column with guard, 98:2 hexane:EtOH, 0.5 mL min⁻¹) 11.5 min (major), 14.3 min (minor) shows 85 % *ee*.

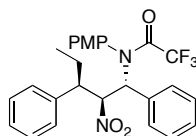
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(1*S*,2*R*,3*S*)-3-(4-methoxy-phenyl)-2-nitro-1-phenyl-pentyl]-acetamide - 231-6



Synthesised *via* general procedures C (231 mg, 69 %) and E (246 mg, 73 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 90:10:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as a yellow oil: R_f 0.18 (10 % EtOAc:petrol); $[\alpha]_D^{22} + 24.8$ (c 0.49, CHCl₃); IR ν_{\max} 3010 (C-H), 2965 (C-H), 2840 (C-H), 1698 (C=O), 1607, 1585, 1553 (NO₂), 1512, 1254 (CF), 1112 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.80 (3H, t, $J = 7.3$, CH₃CH₂), 1.71 (1H, qdd, $J = 14.3$, 11.9, 7.1, CHHCH₃), 2.13 (1H, dqd, $J = 14.2$, 7.1, 2.9, CHHCH₃), 3.14 (1H, ddd, $J = 11.8$, 4.8, 3.0, CHCH₂CH₃), 3.77 (3H, s, OMe), 3.82 (3H, s, OMe), 5.62 (1H, dd, $J = 10.4$, 4.9, CHNO₂), 6.15 (2H, m, HAr and CHNTFA), 6.56 (1H, dd, $J = 8.8$, 2.9, HAr), 6.81 (1H, dd, $J = 8.8$, 2.9, HAr), 6.88-6.97 (5H, m, HAr), 7.15 (2H, dt, $J =$

8.7, 3.1, *HAr*), 7.20 (2H, t, $J = 7.7$, *HAr*), 7.28 (1H, tt, $J = 7.7$, 3.1 *HAr*); ^{13}C NMR (CDCl_3 , 100 MHz) δ 12.2 (CH_3CH_2), 23.2 (CH_2CH_3), 47.2 (CHCH_2CH_3), 55.2 (*OMe*), 55.4 (*OMe*), 63.2 (CHNTFA), 91.7 (CHNO_2), 113.6 (*HAr*), 114.1 (*HAr*), 114.3 ($2 \times \text{HAr}$), 116.2 (q, $J = 290.1$, CF_3), 127.7 (*Ar*), 128.6 (*HAr*), 128.7 (*HAr*), 129.2 (*HAr*), 129.4 ($2 \times \text{HAr}$), 129.7 (*HAr*), 130.5 (*Ar*), 130.7 (*HAr*), 132.2 (*HAr*), 132.3 (*Ar*), 133.2 (*HAr*), 158.0 (q, $J = 35.8$, C=O), 159.2 (*Ar*), 160.2 (*Ar*); ^{19}F (CDCl_3 , 376 MHz) δ -67.2 (3F, s, CF_3); m/z (ESI^+) 539 ($\text{M}+\text{Na}^+$, 68 %), 534 ($\text{M}+\text{NH}_4^+$, 61 %), 517 ($\text{M}+\text{H}^+$, 6 %); HRMS $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_2\text{NaO}_5$ calcd. 539.1764, found 539.1747, $\text{C}_{27}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_5$ calcd. 534.2210, found 534.2202, $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_5$ calcd. 517.1945, found 517.1935; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min^{-1}) 18.3 min (major), 22.8 min (minor) shows 90 % *ee*.

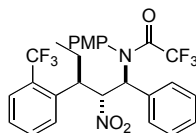
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*R*,2*S*,3*R*)-2-nitro-1,3-diphenyl-pentyl)-acetamide - 225-1



Synthesised *via* general procedures C (243 mg, 75 %), D (231 mg, 71 %) and I (208 mg, 64 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 85:10:5:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 90:0:10:0. Isolated as a 90:0:10:0 mixture of diastereoisomers as a white solid: m.p. 128-130 °C; R_f 0.21 (10 % EtOAc:petrol); $[\alpha]_D^{22}$ -24.1 (c 0.41, CHCl_3); IR ν_{max} 2971 (C-H), 2841 (C-H), 1698 (C=O), 1607, 1555 (NO_2), 1511, 1182 (CF) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.83 (3H, t, $J = 7.3$, CH_3CH_2), 1.77 (1H, ddq, $J = 11.9$, 11.8, 7.2, CHHCH_3), 2.16 (1H, dqd, $J = 13.7$, 7.3, 3.0, CHHCH_3),

3.21 (1H, ddd, $J = 11.8, 4.8, 3.0$, CHCH_2CH_3), 3.81, (3H, s, OMe), 5.66 (1H, dd, $J = 10.5, 4.9$, CHNO_2), 6.18 (2H, d, $J = 10.1$, CHNTFA), 6.56 (1H, dd, $J = 8.8, 2.8$, HAr), 6.83 (2H, m, HAr), 7.15-7.25 (5H, m, HAr), 7.28-7.43 (5H, m, HAr); Minor diastereoisomer - 0.92 (3H, t, $J = 7.4$, CH_3CH_2), 3.35 (1H, m, CHHCH_3), 3.84 (3H, s, OMe), 6.61 (1H, m, CHNTFA) remaining peaks could not be distinguished; ^{13}C NMR (CDCl_3 , 100 MHz) δ 12.2 (CH_3CH_2), 23.1 (CH_2CH_3), 48.0 (CHCH_2CH_3), 55.4 (OMe), 63.5 (CHNTFA), 91.6 (CHNO_2), 116.3 (q, $J = 288.8$, CF_3), 127.7 (HAr), 128.0 (HAr), 128.2 (HAr), 128.6 (HAr), 128.7 (HAr), 128.8 (HAr), 129.0 (HAr), 129.3 (HAr), 129.4 (HAr), 129.7 (HAr), 130.5 (HAr), 132.2 (HAr), 133.2 (HAr), 133.3 (Ar), 134.8 (Ar), 136.6 (Ar), 139.0 (HAr), 158.2 (q, $J = 35.8$, C=O), 160.4 (Ar); Minor diastereoisomer - 12.5 (CH_3CH_2), 26.4 (CH_2CH_3), 48.2 (CHCH_2CH_3), 90.7 (CHNO_2), 116.4 (q, $J = 288.8$, CF_3), 158.3 (q, $J = 35.8$, C=O), 160.4 (Ar) remaining peaks could not be distinguished; ^{19}F NMR (CDCl_3 , 376 MHz) δ -67.0 (3F, s, CF_3); m/z (ESI^+) 509 (100 %, $\text{M}+\text{Na}^+$), 504 (14 %, $\text{M}+\text{NH}_4^+$); HRMS $\text{C}_{26}\text{H}_{25}\text{F}_3\text{N}_2\text{NaO}_4$ calcd. 509.1659, found 509.1653, $\text{C}_{26}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_4$ calcd. 504.2105, found 504.2102; Anal. calcd. for $\text{C}_{26}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4$: C 64.19 %, H 5.18 %, N 5.76 %. Found C 64.17, H 5.22, N 5.63; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min $^{-1}$), 17.5 min (minor), 19.8 (major), shows 85 % *ee*.

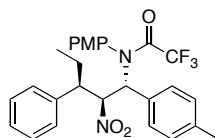
(±)-2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(1*S,2*R**,3*R**)-2-nitro-1-phenyl-3-(2-trifluoromethyl-phenyl)-pentyl]-acetamide - 235**



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 5:10:85:0.

Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 5:0:95:0. Isolated as a 5:0:95:0 mixture of diastereoisomers as an off-white solid (141 mg, 38 %): m.p. 57-59 °C; R_f 0.18 (10 % EtOAc:petrol); IR ν_{max} 2981 (C-H), 2844 (C-H), 1696 (C=O), 1585, 1511 (NO₂), 1311 (NO₂), 1181 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.81 (3H, t, J = 7.4, CH₃CH₂), 1.84-2.07 (2H, m, CH₂CH₃), 3.76, (3H, s, OMe), 3.83 (1H, td, J = 9.1, 4.6, CHCH₂CH₃), 5.94 (1H, d, J = 8.7, CHNTFA), 6.16 (1H, t, J = 8.7, CHNO₂), 6.23 (1H, dd, J = 8.8, 2.2, HAr), 6.57 (1H, dd, J = 8.9, 2.8, HAr), 6.80 (2H, m, HAr), 7.17-7.35 (5H, m, HAr), 7.39 (1H, t, J = 7.1, HAr), 7.56 (2H, m, HAr), 7.68 (1H, d, J = 8.0, HAr); Minor diastereoisomer 2.40 (2H, m, CH₂CH₃), 3.80 (3H, s, OMe), 6.42 (1H, m, HAr), 6.66 (1H, dd, J = 8.8, 2.7, HAr), 6.88 (1H, dd, J = 9.0, 2.8, HAr), 7.10 (2H, m, HAr), 7.76 (1H, d, J = 8.0, HAr) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 100 MHz) δ 10.8 (CH₃CH₂), 26.7 (CH₂CH₃), 43.0 (CHCH₂CH₃), 55.5 (OMe), 65.6 (CHNTFA), 89.6 (CHNO₂), 113.5 (HAr), 114.1 (HAr), 116.1 (q, J = 288.3, CF₃C=O), 124.2 (q, J = 274.0, CF₃Ar), 126.7 (q, J = 6.13, HAr), 127.7 (HAr), 128.1 (HAr), 128.3 (HAr), 128.4 (Ar), 128.6 (HAr), 129.6 (HAr), 129.7 (q, J = 39.9, ArCF₃), 129.7 (q, J = 33.7, HAr), 130.5 (HAr), 130.9 (HAr), 131.9 (HAr), 132.3 (HAr), 132.8 (Ar), 138.0 (Ar), 158.4 (q, J = 35.8, C=O), 160.2 (Ar); Minor diastereoisomer - 23.2 (CH₂CH₃), 90.2 (CHNO₂) remaining peaks could not be distinguished; ¹⁹F NMR (CDCl₃, 376 MHz) δ - 67.6 (3F, s, CF₃C=O), -57.4 (3F, s, CF₃Ar); m/z (ESI⁺) 572 (100 %, M+NH₄⁺), 577 (64 %, M+Na⁺), 555 (6 %, M+H⁺); HRMS C₂₇H₂₅F₆N₂O₄ calcd 555.1713, found 555.1695, C₂₇H₂₈F₆N₃O₄ calcd. 572.1979, found 572.1956, C₂₇H₂₄F₆N₂NaO₄ calcd. 577.1532, found 577.1512.

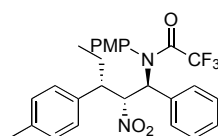
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*R*,2*S*,3*R*)-2-nitro-3-phenyl-1-*p*-tolyl-pentyl)-acetamide - 225-3



Synthesised *via* general procedures C (225 mg, 68 %) and D (213 mg, 64 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 75:15:10:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 90:0:10:0. Isolated as a 95:0:5:0 mixture of diastereoisomers as a yellow oil: R_f 0.36 (10 % EtOAc:petrol): $[\alpha]_D^{22} - 15.0$ (c 0.51, CHCl₃); IR ν_{\max} (CHCl₃) 3010 (C-H), 2969 (C-H), 2842 (C-H), 1697 (C=O), 1605, 1555, 1511 (NO₂), 1182 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.81 (3H, t, $J = 7.3$, CH₃CH₂), 1.80 (1H, ddq, $J = 13.7, 11.9, 7.1$, CHHCH₃), 2.17 (1H, dqd, $J = 13.7, 7.1, 4.4$, CHHCH₃), 2.92 (3H, s, MePh), 3.21 (1H, ddd, $J = 8.7, 4.8, 3.0$, CHCH₂CH₃), 3.79 (3H, s, OMe), 5.65 (1H, dd, $J = 10.5, 4.9$, CHNO₂), 6.12 (1H, d, $J = 10.5$, CHNTFA), 6.23 (1H, d, $J = 7.5$, HAr), 6.60 (1H, dd, $J = 8.9, 2.9$, HAr), 6.79-6.90 (3H, m, HAr), 6.93-7.04 (3H, m, HAr), 7.21-7.26 (2H, m, HAr), 7.33-7.43 (3H, m, HAr); Minor diastereoisomer - 0.90 (3H, t, CH₃CH₂), 2.05 (1H, m, CHHCH₃), 3.32 (1H, m, CHCH₂CH₃), 3.81 (3H, s, OMe), 6.02 (1H, m, HAr), 6.65 (1H, m, HAr), 7.21-7.26 (1H, m, HAr), 7.33-7.43 (2H, m, HAr) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 100 MHz) δ 12.2 (CH₃CH₂), 21.2 (MeAr), 23.0 (CH₂CH₃), 48.0 (CHCH₂CH₃), 63.2 (CHNTFA), 91.7 (CHNO₂), 113.8 (HAr), 114.9 (HAr), 116.3 (q, $J = 288.8$, CF₃), 128.1 (HAr), 128.2 (HAr), 128.9 (HAr), 129.2 (HAr), 129.3 (HAr), 129.4 (HAr), 129.5 (Ar), 129.6 (HAr), 129.8 (HAr), 130.2 (HAr), 130.4 (Ar), 130.5 (HAr), 132.3 (HAr), 139.0 (Ar), 139.4 (Ar), 158.2 (q, $J = 35.8$, C=O), 160.3 (Ar); Minor diastereoisomer 12.5 (CH₃CH₂), 26.4 (CH₂CH₃), 48.2 (CHCH₂CH₃), 90.8 (CHNO₂) remaining peaks could not be

distinguished; ^{19}F NMR (CDCl_3 , 376 MHz) δ – 67.1 (3F, s, CF_3); m/z (ESI^+) 518 (94 %, $\text{M}+\text{NH}_4^+$), 523 (91 %, $\text{M}+\text{Na}^+$), 501 (11 %, $\text{M}+\text{H}^+$); HRMS $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_4$ calcd. 501.1996, found 501.1988, $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_2\text{NaO}_4$ calcd. 532.1815, found 523.1801, $\text{C}_{27}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_4$ calcd. 518.2261, found 518.2247; HPLC measured for the parent nitro-alkane obtained *via* general procedure L (Chiracel OD-H 250 mm column with guard, 98:2 hexane:IPA, 0.5 mL min^{-1}) 18.4 min (major), 21.4 min (minor) shows 91 % *ee*.

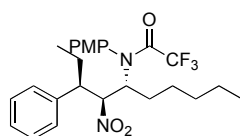
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*S*,2*R*,3*S*)-2-nitro-1-phenyl-3-*p*-tolyl-pentyl)-acetamide - 231-3



Synthesised *via* general procedures C (239 mg, 71 %) and E (241 mg, 72 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 70:15:15:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 80:0:20:0. Isolated as a 85:0:15:0 mixture of diastereoisomers as a yellow solid: m.p. 102-105 °C; R_f 0.26 (10 % EtOAc:petrol); $[\alpha]_D^{22}$ – 33.5 (c 0.50, CHCl_3); IR ν_{max} (CHCl_3) 2970 (C-H), 2841 (C-H), 1697 (C=O), 1554, 1511 (NO_2), 1254 (CF), 1182 (CF), 1112 (CF) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.81 (3H, t, $J = 7.3$, CH_3CH_2), 1.76 (1H, ddq, $J = 13.5, 11.9, 7.2$, CHHCH_3), 2.16 (1H, dqd, $J = 13.7, 7.3, 2.9$, CHHCH_3), 2.39 (3H, s, ArMe), 3.17 (1H, ddd, $J = 11.8, 4.6, 4.4$, CHCH_2CH_3), 3.81 (3H, s, OMe), 5.61 (1H, dd, $J = 10.4, 4.8$, CHNO_2), 6.20 (1H, d, $J = 10.4$, CHNTFA), 6.21 (1H, d, $J = 8.0$, HAr), 6.57 (1H, dd, $J = 8.8, 2.9$, HAr), 6.81 (1H, dd, $J = 8.8, 2.9$, HAr), 6.90 (1H, td, $J = 8.8, 2.4$, HAr), 6.98 (2H, m, HAr), 7.10 (2H, m, HAr), 7.19 (5H, m, HAr); Minor diastereoisomer - 0.91 (3H, $J = 7.3$, CH_3CH_2), 2.03 (1H, m, CHHCH_3), 3.30 (1H, $J = 10.2, 4.8, 4.0$,

CHCH₂CH₃), 3.84 (3H, s, OMe), 5.56 (1H, m, CHNO₂), 6.10 (1H, dd, *J* = 7.0, 2.2, HAr), 6.61 (1H, dd, *J* = 8.9, 2.8, HAr), 7.06 (2H, m, HAr) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 100 MHz) δ 12.2 (CH₃CH₃), 21.1 (MeAr), 22.9 (CH₂CH₃), 47.7 (CHCH₂CH₃), 55.5 (OMe), 63.2 (CHNTFA), 91.7 (CHNO₂), 113.6 (HAr), 114.0 (HAr), 116.2 (q, *J* = 289.8, CF₃), 127.8 (Ar), 128.1 (HAr), 128.6 (HAr), 128.8 (HAr), 129.6 (HAr), 129.2 (HAr), 129.4 (HAr), 129.5 (HAr), 129.7 (HAr), 130.5 (HAr), 132.2 (HAr), 133.3 (HAr), 133.3 (Ar), 135.8 (Ar), 137.7 (Ar) 158.2 (q, *J* = 35.3, C=O), 160.2 (Ar); Minor diastereoisomer - 12.6 (CH₃CH₂), 26.4 (CH₂CH₃), 47.8 (CHCH₂CH₃), 137.9 (Ar), 160.4 (Ar) remaining peaks could not be distinguished; ¹⁹F (CDCl₃, 376 MHz) δ - 67.1 (3F, s, CF₃); m/z (ESI⁺) 523 (M+Na⁺, 100 %), 518 (M+NH₄⁺, 88 %), 501 (M+H⁺, 12 %); HRMS C₂₇H₂₇F₃N₂NaO₄ calcd. 523.1815, found 523.1802, C₂₇H₃₁F₃N₃O₄ calcd. 518.2261, found 518.2250, C₂₇H₂₈F₃N₂O₄ calcd. 501.1986, found 501.1987; Anal. calcd. for C₂₇H₂₇F₃N₂O₄ C 67.79 %, H 5.44 %, N 5.60 %. Found C 64.93 %, H 5.55 %, N 5.38 %; HPLC measured for parent nitro-alkane obtained *via* general procedure M (Chiracel OD-H 250 mm column, 98:2 hexane:IPA, 0.5 mL min⁻¹) 22.9 min (major), 31.0 min (minor) shows 90 % *ee*.

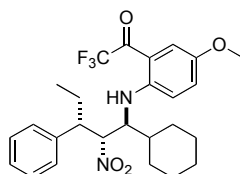
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(*R*)-1-((1*S*,2*R*)-1-nitro-2-phenyl-butyl)-hexyl]-acetamide - 225-4



Synthesised *via* general procedures C (203 mg, 63 %) and D (220 mg, 68 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 95:5:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as a yellow oil: R_f 0.28 (10 % EtOAc:petrol); [α]_D²² +

53.1 (c 0.72, CHCl₃); IR ν_{\max} (CHCl₃) 3053 (C-H), 2986 (C-H), 2306, 1691 (C=O), 1608, 1551, 1512 (NO₂), 1260 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.72 (3H, t, J = 7.3, CH₃), 0.82 (3H, t, J = 7.3, CH₃), 0.86-1.07 (6H, M, 3 \times CH₂), 1.68 (4H, m, 2 \times CH₂), 3.12 (1H, td, J = 10.3, 4.0, CHCH₂CH₃), 3.84 (3H, s, OMe), 4.23 (1H, m, CHNTFA), 5.23 (1H, dd, J = 10.2, 3.9, CHNO₂), 6.86 (2H, m, HAr), 7.00 (2H, m, HAr), 7.19 (2H, m, HAr), 7.32 (1H, m, HAr), 7.38 (2H, m, HAr); ¹³C NMR (CDCl₃, 100 MHz) δ 11.4 (CH₃), 13.9 (CH₃), 22.1 (CH₂), 23.7 (CH₂), 26.0 (CH₂), 27.1 (CH₂), 31.2 (CH₂), 49.2 (CHCH₂CH₃), 55.4 (OMe), 61.1 (CHNTFA), 92.7 (CHNO₂), 113.9 (HAr), 114.3 (HAr), 116.1 (q, J = 288.6, CF₃), 117.5 (Ar), 127.8 (Ar), 128.0 (HAr), 128.3 (HAr), 129.0 (2 \times HAr), 130.9 (HAr), 131.2 (HAr), 137.4 (HAr), 158.3 (q, J = 35.5, C=O), 160.3 (Ar); ¹⁹F (CDCl₃, 376 MHz) δ -67.3 (3F, s, CF₃); m/z (ESI⁺) 503 (M+Na⁺, 100 %), 498 (M+NH₄⁺, 79 %), 481 (M+H⁺, 3 %); HRMS C₂₅H₃₁F₃N₂NaO₄ calcd. 503.2128, found 503.2128, C₂₅H₃₅F₃N₃O₄ calcd. 498.2574, found 498.2571, C₂₅H₃₂F₃N₂O₄ calcd. 481.2309, found 481.2326; HPLC measured for parent nitro-alkane obtained *via* general procedure L (Chiracel OD-H 150 mm column with guard, 98:2 hexane:EtOH, 0.5 mL min⁻¹) 12.7 min (min), 15.6 min (major) shows 90 % *ee*.

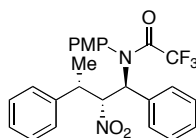
(\pm)-1-[2-((1S*,2R*,3S*)-1-Cyclohexyl-2-nitro-3-phenyl-pentylamino)-5-methoxy-phenyl]-2,2,2-trifluoro-ethanone - 239



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 80:10:10:0. Analysis of the crude mixture after the protection step showed the ratio of

diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as bright orange feathers (95 mg, 29 %): m.p 163 °C deg; Rf 0.22 (10 % EtOAc:petrol); IR ν_{\max} (thin film) 3695 (NH), 2935 (C-H), 1656 (C=O), 1602, 1551 (NO₂), 1152 (CF) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.62 (2H, t, J = 7.3, CH₃), 1.00-1.29 (6H, m, Cy), 1.53-1.77 (6H, m, Cy + CH₂CH₃), 1.93 (1H, m, CyCH), 3.17, (1H, td, J = 10.2, 4.1, CHCH₂CH₃), 3.80 (3H, s, OMe), 3.93 (1H, ddd, J = 10.4, 8.3, 4.7, CHNH), 5.09 (1H, dd, J = 9.7, 4.7, CHNO₂), 6.84 (1H, d, J = 9.7, HAr), 7.14-7.19 (3H, m, HAr), 7.27-7.33 (4H, m, HAr), 9.39 (1H, d, J = 10.2, NH); ¹³C NMR (CDCl₃, 100 MHz) δ 11.6 (CH₃), 24.9 (CH₂), 25.9 (CH₂), 26.0 (CH₂), 26.1 (CH₂), 29.6 (CH₂), 30.8 (CH₂), 41.9 (CHCy), 48.5 (CHCH₂CH₃), 55.8 (OMe), 56.7 (CHNH), 92.8 (CHNO₂), 110.2 (ArCOCF₃), 112.7 (HAr), 113.6 (HAr), 117.4 (q, J = 292.0, CF₃), 127.8 (HAr), 127.9 (HAr), 128.4 (2 \times HAr), 128.7 (2 \times HAr), 138.0 (Ar), 149.0 (Ar), 149.5 (Ar), 180.0 (q, J = 33.0, C=O); ¹⁹F (CDCl₃, 376 MHz) δ -68.9 (3F, s, CF₃); m/z (ESI⁺) 493 (M+H⁺, 44 %) 515 (M+Na⁺, 9 %); HRMS C₂₆H₃₂F₃N₂O₄ calcd. 493.2314, found 493.2303.

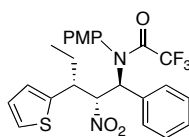
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*S*,2*R*,3*S*)-nitro-1,3-diphenyl-butyl)-acetamide - 231-4



Synthesised *via* general procedures C (209 mg, 66 %) and E (195 mg, 62 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 85:10:5:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 95:0:5:0. Isolated as a single diastereoisomer as a white solid: m.p. 121-123 °C; $[\alpha]_D^{22} + 86.2$ (c 0.84, CHCl₃); Rf 0.22 (15% Et₂O: petrol); IR ν_{\max} (thin film) 3031 (C-H), 2978 (C-H), 1698 (C=O), 1553 (NO₂), 1511 (NO₂), 1256 (C-F), 1209 (C-F), 1181 (C-F), 840

(Ar), 700 (Ar) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.59 (3H, d, $J = 7.1$, CH_3), 3.64 (1H, qd, $J = 7.7$, 4.3, CHCH_3), 3.80 (3H, s, OMe), 5.69 (1H dd, $J = 10.9$, 4.4, CHNO_2), 6.18 (1H, d, $J = 10.7$, CHNTFA), 6.24 (1H, m, HAr), 6.80-6.91 (2H, m, HAr), 7.06 (2H, d, $J = 7.3$, HAr), 7.22 (2H, m, HAr), 7.28-7.41 (7H, m, HAr); Minor diastereoisomer - 1.67 (3H, d, $J = 7.2$, CH_3), 3.82 (3H, s, OMe), 5.52 (1H, m, CHNO_2), 5.98 (1H, m, CHNTFA), 6.05 (1H, m, HAr) remaining peaks could not be distinguished; ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.8 (CH_3), 40.3 (CHMe), 55.7 (OMe), 63.1 (CHNTFA), 91.8 (CHNO_2), 113.8 (HAr), 114.1 (HAr), 116.4 (q, $J = 288.6$, CF_3), 127.4 ($\text{HAr} \times 2$), 127.8 (HAr), 128.2 (HAr), 128.8 ($\text{HAr} \times 2$), 129.5 (HAr), 129.6 (HAr), 130.4 (HAr), 130.6 (HAr), 132.3 (HAr), 133.7 (Ar), 134.5 (Ar), 141.1 (Ar), 158.3 (q, $J = 35.4$, C=O), 160.4 (Ar); ^{19}F (CDCl_3 , 282 MHz) δ - 67.5 (3F, s, CF_3); m/z (ESI^+) 472 ($\text{M}+\text{H}^+$, 24 %); HRMS $\text{C}_{25}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$ calcd. 472.16043, found 472.16103; Anal. Calcd. For $\text{C}_{25}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$ C 63.56 %, H 4.91 %, N 5.93 %. Found C 63.72 %, H 4.98 %, N 5.89 %; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min^{-1}) 19.9 min (major), 21.3 min (minor) shows 98 % *ee*.

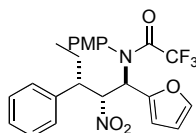
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*S*,2*R*,3*R*)-2-nitro-1-phenyl-3-thiophen-2-yl-pentyl)-acetamide - 231-7



Synthesised *via* general procedures C (281 mg, 85 %) and E (264 mg, 80 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 80:10:10:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 90:0:10:0. Isolated as a 90:0:10:0 mixture of diastereoisomers as a white crystalline solid: mp 132-234

°C; $[\alpha]_D^{16} + 25.4$ (c 0.66, DCM); Rf 0.13 (8% acetone: petrol); IR ν_{\max} (thin film) 3065 (C-H), 2971 (C-H), 2877 (C-H), 1698 (C=O), 1553 (NO₂), 1362 (NO₂), 1208 (C-F), 1168 (C-F), 839 (Ar), 699 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (3H, t, $J = 7.1$, CH₃CH₂), 1.72 (1H, ddq, $J = 13.7, 11.7, 7.1$, CHHCH₃), 2.37 (1H, dqd, $J = 13.7, 7.3, 2.6$, CHHCH₃), 3.53 (1H, dt, $J = 11.6, 3.6$, CHCH₂CH₃), 3.81 (3H, s, OMe), 5.54 (1H dd, $J = 11.0, 3.6$, CHNO₂), 6.11 (1H, m, HAr), 6.41 (1H, d, $J = 11.0$, CHNTFA), 6.58 (1H, dd, $J = 8.9, 2.9$, HAr), 6.86-6.95 (2H, m, HAr), 6.98-7.13 (3H, m, HAr), 7.22 (2H, m, HAr), 7.26-7.37 (3H, m, HAr); Minor diastereoisomer - 1.01 (3H, t, $J = 7.1$, CH₃) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 125 MHz) δ 12.6 (CH₃), 24.0 (CH₂CH₃), 43.1 (CHCH₂CH₃), 55.5 (OMe), 61.5 (CHNTFA), 91.6 (CHNO₂), 113.8 (HAr), 114.2 (HAr), 116.2 (q, $J = 286$, CF₃), 124.7 (HAr), 125.7 (HAr), 127.0 (Ar), 127.4 (HAr), 128.8 (HAr \times 2), 12.3 (HAr \times 2), 129.5 (HAr), 130.5 (HAr), 132.6 (HAr), 133.3 (Ar), 142.0 (Ar), 158.3 (q, $J = 35$, C=O), 160.4 (Ar); ¹⁹F (CDCl₃, 282 MHz) δ - 67.5 (3F, s, CF₃); m/z (FAB⁺) 493 (M+H⁺, 41 %); HRMS C₂₄H₂₄F₃N₂O₄S calcd. 493.14089, found 493.14149; Anal. calcd. for C₂₄H₂₃F₃N₂O₄S C 58.53 %, H 4.71 %, N 5.69 %. Found C 58.57 %, H 4.70 %, N 5.63 %; HPLC measured for parent nitro-alkane obtained *via* general procedure L (Chiracel OD-H 250 mm column with guard, 99:1 hexane:IPA, 0.5 mL min⁻¹) 37.4 min (major), 38.4 min (minor) shows 90 % *ee*.

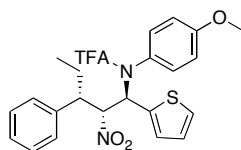
(±)-2,2,2-Trifluoro-N-((1S,2R,3S)-1-furan-2-yl-2-nitro-3-phenyl-pentyl)-N-(4-methoxy-phenyl)-acetamide - 231-1



Synthesised *via* general procedures C (226 mg, 71 %) and E (220 mg, 69 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of

diastereoisomers to be 90:10:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as a white crystalline solid: m.p. 179-182 °C; R_f 0.11 (10% acetone:petrol); IR ν_{max} (thin film) 3033 (C-H), 2968 (C-H), 2879 (C-H), 1696 (C=O), 1555 (NO₂), 1367 (NO₂), 1208 (C-F), 1159 (C-F), 1181 (C-F), 839 (Ar), 745 (Ar), 701 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.70 (3H, t, J = 7.3, CH₃CH₂), 1.70 (1H, ddq, J = 14.3, 11.5, 7.2, CHHCH₃), 1.86 (1H, dqd, J = 13.4, 7.3, 3.1, CHHCH₃), 3.13 (1H, ddd, J = 11.3, 8.5, 3.1, CHCH₂CH₃), 3.75 (3H, s, OMe), 5.64 (1H, apt t, J = 8.1, CHNO₂), 5.89 (1H, d, J = 11.0, CHNTFA), 6.20 (1H, dd, J = 3.3, 1.8, HAr), 6.29 (2H, m, HAr), 6.55 (1H, m, HAr), 6.79 (1H, dd, J = 8.7, 2.2, HAr), 7.04 (2H, m, HAr), 7.22-7.36 (5H, m, HAr); ¹³C NMR (CDCl₃, 125 MHz) δ 11.7 (CH₃), 24.8 (CH₂CH₃), 48.2 (CHCH₂CH₃), 55.4 (OMe), 57.8 (CHNTFA), 90.1 (CHNO₂), 111.0 (HAr), 113.5 (HAr \times 2), 113.6 (HAr), 114.0 (HAr), 115.9 (q, J = 288.5, CF₃), 127.9 (Ar), 128.0 (HAr \times 2), 129.0 (HAr \times 2), 130.4 (HAr), 130.9 (HAr), 137.8 (Ar), 142.7 (Ar), 145.0 (HAr), 157.8 (q, J = 33.8, C=O), 160.1 (Ar); ¹⁹F (CDCl₃, 282 MHz) δ -68.0 (3F, s, CF₃); m/z (Cl⁺) 477 (M+H⁺, 34 %); HRMS C₂₄H₂₄F₃N₂O₅ calcd. 477.16372, found 477.16435.

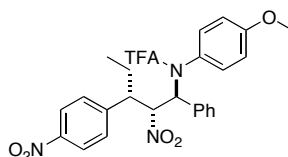
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*R*,2*R*,3*S*)-2-nitro-3-phenyl-1-thiophen-2-yl-pentyl)-acetamide - 231-2



Synthesised *via* general procedures C (223 mg, 68 %) and E (244 mg, 74 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 95:5:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as

a single diastereoisomer as a yellow oil: Rf 0.24 (15% Et₂O:petrol): $[\alpha]_D^{16} + 16.7$ (c 0.54, DCM); IR ν_{\max} (thin film) 2973 (C-H), 2840 (C-H), 1699 (C=O), 1554 (NO₂), 1511 (NO₂), 1255 (C-F), 1208 (C-F), 1181 (C-F), 839 (Ar), 700 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.76 (3H, t, $J = 7.2$, CH₃CH₂), 1.74 (1H, ddq, $J = 13.7, 11.5, 7.4$, CHHCH₃), 1.94 (1H, dqd, $J = 13.7, 7.3, 3.1$, CHHCH₃), 3.14 (1H, ddd, $J = 10.9, 7.0, 3.1$, CHCH₂CH₃), 3.77 (3H, s, OMe), 5.78 (1H, dd, $J = 8.5, 7.2$ CHNO₂), 6.03 (1H, d, $J = 8.5$, CHNTFA), 6.40 (1H, m, HAr), 6.63 (2H, m, HAr), 6.80 (2H, m, HAr), 6.93 (1H, m, HAr), 7.12 (2H, d, $J = 7.3$, HAr), 7.16-7.37 (4H, m, HAr); Minor diastereoisomer - 0.84 (3H, t, $J = 7.4$, CH₃CH₂), 2.01 (1H, m, CHHCH₃), 3.24 (1H, m, CHCH₂CH₃), 3.80 (3H, s, OMe), 5.64 (1H, m, CHNO₂), 6.16 (1H, m, CHNTFA) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 125 MHz) δ 11.8 (CH₃), 24.0 (CH₂CH₃), 48.3 (CHCH₂CH₃), 55.5 (OMe), 60.1 (CHNTFA), 92.1 (CHNO₂), 113.7 (HAr), 114.1 (HAr), 116.1 (q, $J = 288.9$, CF₃), 126.4 (Ar), 126.6 (HAr), 127.5 (HAr), 127.9 (HAr), 128.1 (HAr), 128.4 (HAr), 128.9 (HAr), 129.4 (HAr), 130.5 (HAr), 131.3 (HAr), 133.5 (Ar), 136.4.0 (HAr), 138.6 (Ar), 157.9 (q, $J = 33.5$, C=O), 160.4 (Ar); Minor diastereoisomer - 12.2 (CH₃), 23.9 (CH₂CH₃), 91.6 (CHNO₂), 135.2 (HAr), 136.4 (Ar) 138.0 (HAr) remaining peaks could not be distinguished; ¹⁹F (CDCl₃, 282 MHz) δ - 68.0 (3F, s, CF₃); m/z (CI⁺) 493 (M+H⁺, 53 %); HRMS C₂₄H₂₄F₃N₂O₄S calcd. 493.14088, found 493.13972; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min⁻¹) 18.3 min (major), 20.2 min (minor) shows 95 % *ee*.

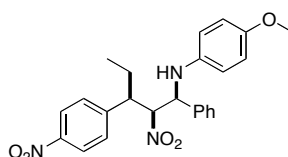
(±)-2,2,2-Trifluoro-N-(4-methoxy-phenyl)-N-[(1S*,2R*,3S*)-2-nitro-3-(4-nitro-phenyl)-1-phenyl-pentyl]-acetamide - 237-2



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 75:5:20:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 80:0:20:0. Isolated as a 90:0:10:0 mixture of diastereoisomers as a colourless oil (136 mg, 38 %): R_f 0.20 (15 % Et₂O:petrol); IR ν_{max} (thin film) 3079 (C-H), 2971 (C-H), 2841 (C-H), 1695 (C=O), 1552 (NO₂), 1509 (NO₂), 1347 (NO₂), 1253 (C-F), 1207 (C-F), 732 (Ar), 699 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.83 (3H, t, J = 7.3, CH₃CH₂), 1.81 (1H, ddq, J = 14.1, 11.9, 7.1, CHHCH₃), 2.21 (1H, dqd, J = 14.3, 7.3, 2.8, CHHCH₃), 3.32 (1H, ddd, J = 11.8, 4.3, 3.1, CHCH₂CH₃), 3.79 (3H, s, OMe), 5.77 (1H, dd, J = 10.1, 4.5 CHNO₂), 5.88 (1H, d, J = 9.9, CHNTFA), 6.34 (1H, d, J = 7.7, HAr), 6.63 (1H, dd, J = 8.8, 2.3, HAr), 6.84 (2H, m, HAr), 7.00 (2H, d, J = 7.6, HAr), 7.20 (2H, d, J = 7.7, HAr), 7.30 (1H, t, J = 7.5, HAr), 7.38 (2H, d, J = 8.7, HAr), 8.24 (2H, d, J = 8.8, HAr); Minor diastereoisomer - 0.72 (3H, t, J = 7.4, CH₃CH₂), 1.65 (1H, m, CHHCH₃), 3.25 (1H, td, J = 10.8, 3.4, CHCH₂CH₃), 3.81 (3H, s, OMe), 5.62 (1H, dd, J = 11.0, 3.5, CHNO₂), 7.52 (2H, d, J = 8.7, HAr), 8.28 (2H, d, J = 8.7, HAr) remaining peaks could not be distinguished; ¹³C NMR (CDCl₃, 125 MHz) δ 12.2 (CH₃), 22.7 (CH₂CH₃), 47.7 (CHCH₂CH₃), 55.6 (OMe), 64.4 (CHNTFA), 91.1 (CHNO₂), 112.7 (HAr), 113.9 (HAr), 116.1 (q, J = 288.6, CF₃), 124.2 (HAr \times 2), 128.9 (HAr \times 2), 129.3 (HAr \times 2), 129.6 (Ar), 129.8 (HAr \times 2), 130.4 (HAr), 131.6 (HAr), 132.9 (HAr), 145.0 (Ar), 146.3 (Ar), 147.7 (Ar), 158.3 (q, J = 35.8, C=O), 160.1 (Ar); Minor diastereoisomer - 11.2

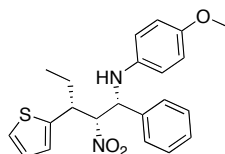
(CH₃), 26.8 (CH₂), 48.3 (CHCH₂CH₃), 55.0 (OMe), 90.7 (CHNO₂) remaining peaks could not be distinguished; ¹⁹F (CDCl₃, 282 MHz) δ – 67.7 (3F, s, CF₃); m/z (EI⁺) 531 (M⁺, 68 %); HRMS C₂₆H₂₄F₃N₃O₆ calcd. 531.16117 found 531.16121.

(±)-(4-Methoxy-phenyl)-[(1S*,2S*,3R*)-2-nitro-3-(4-nitro-phenyl)-1-phenyl-pentyl]-amine - 233-5

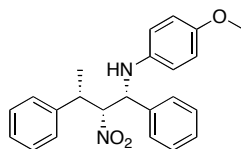


Synthesised *via* general procedure K. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 10:90:0:0. Isolated as a single diastereoisomer as an orange solid (157 mg, 54 %): m.p. 141–143 °C; R_f 0.16 (15 % acetone:petrol); IR ν_{max} (thin film) 3063 (C-H), 2968 (C-H), 2936 (C-H), 1551 (NO₂), 1509 (NO₂), 1345 (NO₂), 699 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.73 (3H, t, *J* = 7.3, CH₃CH₂), 1.73 (1H, ddq, *J* = 13.8, 7.3, 3.8, CHHCH₃), 1.81 (1H, dqd, *J* = 13.8, 11.4, 7.3, CHHCH₃), 3.67 (3H, s, OMe), 3.78 (1H, td, *J* = 11.1, 3.7, CHCH₂CH₃), 4.14 (1H, dd, *J* = 10.8, 4.0 CHNO₂), 5.04 (1H, d, *J* = 10.9, CHNTFA), 6.27 (2H, m, HAr), 6.43 (2H, m, HAr), 7.06 (2H, m, HAr), 7.02–7.27 (3H, m, HAr), 7.43 (2H, m, HAr), 8.18 (2H, m, HAr); ¹³C NMR (CDCl₃, 125 MHz) δ 11.2 (CH₃), 24.7 (CH₂CH₃), 47.6 (CHCH₂CH₃), 55.2 (OMe), 57.0 (CHNTFA), 97.6 (CHNO₂), 114.4 (HAr × 2), 114.5 (HAr × 2), 123.9 (HAr × 2), 125.7 (HAr × 2), 128.0 (HAr), 128.7 (HAr × 2), 129.1 (HAr × 2), 137.0 (Ar), 139.1 (Ar), 145.5 (Ar), 147.2 (Ar), 152.3 (Ar); m/z (CI⁺) 435 (M⁺, 29 %); HRMS C₂₄H₂₅N₃O₅ calcd. 435.17887, found 435.17926.

(4-Methoxy-phenyl)-((1R,2R,3R)-2-nitro-1-phenyl-3-thiophen-2-yl-pentyl)-amine - 233-2

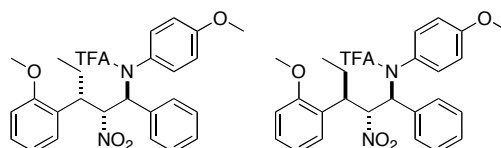


Synthesised *via* general procedures F (188 mg, 71 %) and G (204 mg, 77 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 5:95:0:0. Isolated as a single diastereoisomer as a yellow solid: m.p. 122-125 °C; $[\alpha]_D^{16} + 15.7$ (c 0.83, DCM); Rf 0.14 (15 % acetone:petrol); IR ν_{\max} (thin film) 3028 (C-H), 2967 (C-H), 2934 (C-H), 2833 (C-H), 1551 (NO₂), 1512 (NO₂), 1364 (NO₂), 1242, 819 (C-H), 699 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.85 (3H, t, $J = 7.2$, CH₃CH₂), 1.70 (2H, m, CH₂CH₃), 3.68 (3H, s, OMe), 3.97 (1H, ddd, $J = 11.0, 8.3, 6.7$, CHCH₂CH₃), 4.36 (1H, d, $J = 3.5$ CHNH), 4.91 (1H, dd, $J = 11.0, 3.6$ CHNO₂), 5.13 (1H, brs, NH), 6.34 (2H, m, HAr), 6.64 (2H, m, HAr), 6.88 (1H, dd, $J = 3.5, 1.0$, HAr), 6.94 (1H, dd, $J = 5.1, 3.5$, HAr), 7.09 (2H, m, HAr), 7.15 (4H, m, HAr); ¹³C NMR (CDCl₃, 125 MHz) δ 11.6 (CH₃), 26.8 (CH₂CH₃), 43.7 (CHCH₂CH₃), 55.6 (OMe), 57.1 (CHNH), 98.9 (CHNO₂), 114.8 (HAr \times 2), 125.2 (HAr), 126.2 (HAr \times 2), 127.3 (HAr), 127.5 (HAr \times 2), 128.1 (HAr \times 2), 129.0 (HAr \times 2), 138.0 (Ar), 140.1 (Ar), 141.0 (Ar), 152.3 (Ar); m/z (EI⁺) 396 (M⁺, 22 %); HRMS C₂₂H₂₄N₂O₃S calcd. 396.15021, found 396.15078; Anal. calcd. for C₂₂H₂₄N₂O₃S C 66.64 %, H 6.10 %, N 7.07 %. Found C 66.52 %, H 6.04 %, N 6.96 %; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min⁻¹) 27.2 min (major), 29.3 min (minor) shows 86 % *ee*.

(4-Methoxy-phenyl)-((1R,2R,3S)-2-nitro-1,3-diphenyl-butyl)-amine - 233-1

Synthesised *via* general procedures F (200 mg, 79 %) and G (182 mg, 72 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 95:5:0:0. Isolated as a single diastereoisomer as a pale yellow oil: $[\alpha]_D^{16} + 11.4$ (c 0.67, DCM); Rf 0.31 (15 % acetone: petrol); IR ν_{\max} (thin film) 3061 (C-H), 3029 (C-H), 1549 (NO₂), 1509 (NO₂), 1242, 819 (C-H), 699 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.37 (3H, d, $J = 7.0$ CH₃), 3.68 (3H, s, OMe), 3.87 (1H, qd, $J = 10.9, 6.9$ CHCH₃), 4.26 (1H, dd, $J = 10.6, 3.7$ CHNH), 4.88 (1H, dd, $J = 10.9, 3.8$, CHNO₂), 5.11 (1H, d, $J = 10.5$, NH), 6.31 (2H, m, HAr), 6.64 (2H, m, HAr), 7.06 (2H, m, HAr), 7.17-7.35 (8H, m, HAr); ¹³C NMR (CDCl₃, 125 MHz) δ 18.3 (CH₃), 40.6 (CHCH₃), 55.7 (OMe), 57.1 (CHNH), 99.7 (CHNO₂), 114.5 (HAr \times 2), 114.8 (HAr \times 2), 126.2 (HAr \times 2), 127.8 (HAr \times 2), 127.9 (HAr), 128.1 (HAr), 129.0 (HAr \times 2), 129.2 (HAr \times 2), 138.3 (Ar), 140.0 (Ar), 140.3 (Ar), 152.3 (Ar); m/z (EI⁺) 376 (M⁺, 64 %); HRMS C₂₃H₂₄N₂O₃ calcd. 376.17814, found 376.17834; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane:IPA, 0.5 mL min⁻¹) 26.3 min (major), 28.8 min (minor) shows 93 % *ee*.

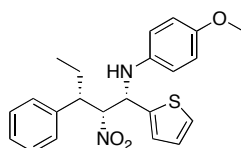
(±)-2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(1*S,2*R**,3*S**)-(2-methoxy-phenyl)-2-nitro-1-phenyl-pentyl]-acetamide & (±)-2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(1*S**,2*R**,3*R**)-(2-methoxy-phenyl)-2-nitro-1-phenyl-pentyl]-acetamide - 237-3**



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 50:0:50:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 50:0:50:0. Isolated as two separate single diastereoisomers as white solids (8 mg, 2 %): m.p. 119-123 °C; R_f 0.20 (15 % Et₂O:petrol); IR ν_{max} (thin film) 2968 (C-H), 1698 (C=O), 1551 (NO₂), 1512 (NO₂), 1245 (C-F), 1207 (C-F), 1182, 757 (Ar), 733 (Ar) cm⁻¹; ¹H NMR first eluted diastereoisomer - (CDCl₃, 500 MHz) δ 0.80 (3H, t, *J* = 7.2, CH₃CH₂), 1.84 (1H, ddq, *J* = 13.8, 7.2, 6.7, CHHCH₃), 2.34 (1H, brs, CHHCH₃), 3.78 (3H, s, OMe), 3.90 (1H, m, CHCH₂CH₃), 3.93 (3H, s, OMe), 5.48 (1H, apt. d, *J* = 8.6, CHNO₂), 6.06 (1H, d, *J* = 8.1, HAr), 6.53 (2H, m, CHNTFA & HAr), 6.84 (1H, dd, *J* = 8.8, 2.7, HAr), 6.93-7.00 (4H, m, HAr), 7.07 (1H, d, *J* = 7.4, HAr), 7.16 (2H, t, *J* = 7.5, HAr), 7.24-7.35 (3H, m, HAr); Second eluted diastereoisomer - ¹H NMR (CDCl₃, 600 MHz, 327 K) δ 0.86 (3H, t, *J* = 7.3, CH₃), 1.90 (1H, brs, CHHCH₃), 1.98 (1H, dqd, *J* = 14.4, 7.3, 5.2, CHHCH₃), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 4.15 (1H, brs, CHCH₂CH₃), 5.74 (1H, brs, CHNO₂), 5.93 (1H, brs, CHNTFA), 6.60 (1H, d, *J* = 8.4, HAr), 6.81-6.98 (3H, m, HAr), 7.08 (2H, m, HAr), 7.16 (1H, m, HAr), 7.19 (2H, t, *J* = 7.8, HAr), 7.26 (2H, m, HAr), 7.33 (1H, m, HAr), 7.46 (1H, m, HAr); ¹³C NMR First eluted diastereoisomer - (CDCl₃, 125 MHz) δ 12.2 (CH₃), 21.4 (CH₂CH₃), 44.6 (CHCH₂CH₃), 55.3

(OMe), 55.5 (OMe), 61.4 (CHNTFA), 90.2 (CHNO₂), 110.7 (HAr), 113.6 (HAr), 113.7 (HAr), 116.4 (q, $J = 287.9$, CF₃), 121.2 (HAr), 127.0 (Ar), 127.4 (HAr), 128.5 (HAr \times 2), 128.7 (HAr), 129.2 (HAr \times 2), 129.4 (HAr \times 2), 130.8 (HAr), 132.9 (Ar), 133.5 (Ar), 157.0 (Ar), 158.0 (q, $J = 33.3$, C=O), 160.2 (Ar); Second eluted diastereoisomer (CDCl₃, 150 MHz) δ 11.5 (CH₃), 29.5 (CH₂CH₃), 37.4 (CHCH₂CH₃), 55.6 (OMe), 55.9 (OMe), 62.9 (CHNTFA), 90.7 (CHNO₂), 111.0 (HAr), 113.9 (HAr), 114.2 (HAr), 114.8 (HAr \times 2), 116.8 (q, $J = 289.0$, CF₃), 121.1 (HAr \times 2), 122.5 (HAr \times 2), 126.0 (Ar), 128.7 (HAr \times 2), 129.1 (HAr), 129.3 (HAr), 130.9 (Ar), 135.7 (Ar), 158.1 (q, $J = 35.5$, C=O), 158.4 (Ar), 160.5 (Ar); ¹⁹F (CDCl₃, 282 MHz) δ - 67.7 (3F, s, CF₃); m/z (EI⁺) 516 (M⁺, 6 %); HRMS C₂₇H₂₇F₃N₂O₅ calcd. 516.18666 found 516.18646.

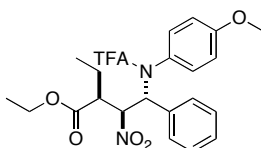
(4-Methoxy-phenyl)-((1S,2R,3S,-)2-nitro-3-phenyl-1-thiophen-2-yl-pentyl)-amine - 233-3



Synthesised *via* general procedures F (177 mg, 67 %) and H (173 mg, 65 %). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 5:95:0:0. Isolated as a single diastereoisomer as a yellow solid: m.p. 127-130 °C; $[\alpha]_D^{16} + 9.5$ (c 0.34, DCM) Rf 0.14 (15 % acetone:petrol); IR ν_{\max} (thin film) 3067 (C-H), 2967 (C-H), 2933 (C-H), 1551 (NO₂), 1511 (NO₂), 1243, 1037, 820 (C-H), 701 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.73 (3H, t, $J = 7.3$, CH₃), 1.67 (1H, dqd, $J = 13.4, 7.3, 3.7$, CHHCH₃), 1.80 (1H, ddq, $J = 13.4, 11.6, 7.2$, CHHCH₃), 3.58 (1H, td, $J = 11.3, 3.5$, CHCH₂CH₃), 3.70 (3H, s, OMe), 4.50 (1H, dd, $J = 10.3, 3.5$, CHNH), 4.92 (1H, d, 10.7, NH), 5.06 (1H, dd, $J = 10.9, 3.7$, CHNO₂), 6.32 (2H, m, ArH), 6.66 (2H, m, ArH), 6.80 (1H, ArH), 6.86 (1H, m, ArH), 7.13 (1H, m, ArH), 7.18 (2H, m,

ArH), 7.30 (3H, m, *ArH*); ^{13}C NMR (CDCl_3 , 125 MHz) δ 11.5 (CH_3), 24.8 (CH_2), 47.5 (CHCH_2CH_3), 53.7 (CHNH), 55.2 (*OMe*), 98.2 (CHNO_2), 114.1 (*ArH* \times 2), 114.7 (*ArH* \times 2), 122.0 (*ArH*), 124.3 (*ArH*), 124.6 (*ArH*), 126.6 (*ArH*), 127.3 (*ArH*), 128.1 (*ArH*), 131.2 (*ArH* \times 2), 137.5 (*Ar*), 139.5 (*Ar*), 142.4 (*Ar*), 154.3 (*Ar*); m/z (EI^+) 396 (M^+ , 8 %); HRMS $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ calcd. 396.15021, found 396.14952; HPLC (Chiracel OD-H 150 mm column, 99.5:0.5 hexane:IPA, 0.5 mL min^{-1}) 21.0 min (major), 24.8 min (minor) shows 93 % *ee*.

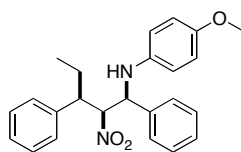
(\pm)-(2*S,3*R**,4*S**)-2-Ethyl-4[(4-methoxy-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-3-nitro-4-phenyl-butyric acid ethyl ester - 241**



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 60:10:30:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 65:0:35:0. Isolated as a 65:0:35:0 mixture of diastereoisomers as a yellow oil (120 mg, 37 %): R_f 0.14 (10 % acetone:petrol); IR ν_{max} (thin film) 2974 (C-H), 2938 (C-H), 2842 (C-H), 1730 (C=O), 1698 (C=O), 1557 (NO_2), 1510 (NO_2), 1254 (C-F), 1205 (C-F), 1180, 1156, 734 (*Ar*), 701 (*Ar*) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.08 (3H, t, $J = 7.4$, CH_3CH_2), 1.29 (3H, t, $J = 7.2$, $\text{CH}_3\text{CH}_2\text{O}$), 1.78 (1H, dqd, $J = 13.2$, 7.4, 5.8, CHHCH_3), 2.02 (1H, ddq, $J = 14.1$, 9.1, 7.4, CHHCH_3), 3.01 (1H, ddd, $J = 9.1$, 5.6, 3.6, CHC=O), 3.79 (3H, s, *OMe*), 4.20-4.35 (2H, m, OCH_2CH_3), 5.61 (1H, m, CHNO_2), 6.01 (1H, dd, $J = 10.6$, 3.2, CHNTFA), 6.49-6.78 (2H, m, *HAr*), 6.91-7.06 (2H, m, *HAr*), 7.18-7.32 (5H, m, *HAr*); Minor diastereoisomer - 1.03 (3H, t, $J = 7.3$, CH_3CH_2), 1.37 (3H, t, $J = 7.2$, $\text{CH}_3\text{CH}_2\text{O}$), 1.70 (1H, dqd, $J = 11.3$, 7.1,

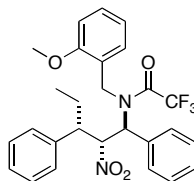
4.2, *CHHCH*₃), 1.96 (1H, m, *CHHCH*₃), 2.96 (1H, m, *CHC=O*), 3.79, (3H, s, *OMe*), 4.20-4.35 (2H, m, *CH*₂O), 5.59 (1H, m, *CHNO*₂), 6.04 (1H, d, *J* = 9.5, *CHNTFA*) remaining signals could not be distinguished; ¹³C NMR (CDCl₃, 125 MHz) δ 11.9 (*CH*₃), 14.1 (*CH*₃*CH*₂O), 22.8 (*CH*₂*CH*₃), 47.7 (*CHCH*₂*CH*₃), 55.5 (*OMe*), 61.8 (*OCH*₂*CH*₃), 66.0 (*CHNTFA*), 88.3 (*CHNO*₂), 113.5 (*HAr*), 113.8 (*HAr*), 113.9 (*HAr*), 116.2 (q, *J* = 288.7, *CF*₃), 128.9 (*HAr*), 129.4 (*HAr* × 2), 129.7 (*HAr*), 130.6 (*HAr*), 131.6 (*HAr*), 136.1 (*C*Ar), 138.1 (*C*Ar), 158.1 (q, *J* = 35.7, *C=O*), 160.4 (*C*Ar), 171.4 (*C=O*); Minor diastereoisomer - 12.4 (*CH*₃), 14.1 (*CH*₃*CH*₂O), 20.1 (*CH*₂*CH*₃), 48.0 (*CHCH*₂*CH*₃), 61.9 (*OCH*₂*CH*₃), 87.1 (*CHNO*₂), 116.4 (q, *J* = 288.7, *CF*₃), 130.7 (*HAr*) remaining signals could not be distinguished; ¹⁹F (CDCl₃, 282 MHz) δ - 67.7 (3F, s, *CF*₃); m/z (EI⁺) 482 (*M*⁺, 8 %); HRMS C₂₃H₂₅F₃N₂O₆ calcd. 482.16592 found 482.16656.

(±)-(4-Methoxy-phenyl)-((1*S,2*S**,3*R**)-2-nitro-1,3-diphenyl-pentyl)-amine - 233-4⁹³**



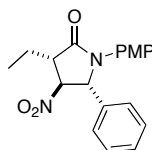
Synthesised *via* general procedure J. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 15:85:0:0. Isolated as a single diastereoisomer as a white solid (164 mg, 63 %): m.p. 127-129 °C; ¹H NMR (CDCl₃, 400 MHz) δ 0.76 (3H, t, *J* = 7.3, *CH*₃), 1.66 (1H, dqd, *J* = 13.5, 7.3, 3.6, *CHHCH*₃), 1.79 (1H, ddq, *J* = 13.5, 11.6, 7.2, *CHHCH*₃), 3.64 (1H, apt td, *J* = 11.3, 3.5, *CHCH*₂*CH*₃), 3.69 (3H, s, *OMe*), 4.24 (1H, dd, *J* = 10.5, 3.5, *CHNH*), 4.97 (1H, dd, *J* = 11.1, 3.6, *CHNO*₂), 5.12 (1H, d, *J* = 10.5, *NH*), 6.29 (2H, m, *HAr*), 6.63 (2H, m, *HAr*), 7.08 (2H, m, *HAr*), 7.22 (5H, m, *HAr*), 7.33 (3H, m, *HAr*). All other data in agreement with literature.⁹³

(±)-2,2,2-Trifluoro-*N*-(2-Methoxy-benzyl)-*N*-((1*R,2*S**,3*R**)-2-nitro-1,3-diphenyl-pentyl)-acetamide - 220**



Synthesised *via* general procedure C. Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 50:50:0:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as a white crystalline solid (170 mg, 34 %): m.p. 112-114 °C; Rf 0.27 (15 % Et₂O: petrol); IR ν_{max} (thin film) 3317 (C-H), 2968 (C-H), 2942 (C-H), 1711 (C=O), 1604, 1553 (NO₂), 1495, 1247 (C-F), 1198 (C-F), 1181 (C-F), 1162, 754 (Ar), 702 (Ar) cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 0.64 (3H, t, J = 7.3, CH₃), 1.42 (1H, dqd, J = 14.6, 7.3, 3.1, CHHCH₃), 1.56 (1H, ddq, J = 14.1, 12.0, 7.1, CHHCH₃), 2.95 (1H, ddd, J = 11.8, 4.6, 3.1, CHCH₂CH₃), 3.82 (3H, s, OMe), 4.53 (1H, d, J = 15.7, CHHAr), 4.64 (1H, d, J = 15.6, CHHAr), 5.09 (1H, d, J = 10.6, CHNTFA), 6.14 (1H, dd, J = 10.5, 4.8, CHNO₂), 6.85 (1H, d, J = 8.4, HAr), 6.88 (1H, td, J = 7.5, 1.0, HAr), 7.08 (1H, m, HAr), 7.11 - 7.20 (4H, m, HAr), 7.21 - 7.27 (3H, m, HAr), 7.31 - 7.35 (4H, m, HAr); ¹³C NMR (CDCl₃, 125 MHz) δ 12.1 (CH₃), 22.0 (CH₂CH₃), 46.8 (CH₂Ar), 48.0 (CHCH₂CH₃), 55.4 (OMe), 63.7 (CHNTFA), 93.2 (CHNO₂), 110.8 (HAr), 116.7 (q, J = 288.7, CF₃), 121.0 (HAr), 122.0 (Ar), 127.8 (HAr), 128.1 (HAr \times 2), 128.5 (HAr \times 2), 128.9 (HAr \times 2), 129.1 (HAr), 129.6 (HAr \times 2), 130.3 (HAr), 130.5 (HAr), 134.8 (Ar), 138.6 (Ar), 157.6 (Ar), 158.2 (q, J = 36.1, C=O); m/z (EI⁺) 500 (M⁺, 14 %); HRMS C₂₇H₂₇F₃N₂O₄ calcd. 500.19174 found 500.19183.

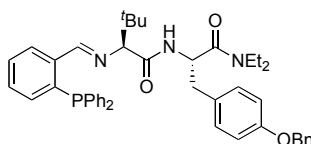
(±)-(3S*,4S*,5R*)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-phenyl-pyrrolidin-2-one - 242-a⁹³



Synthesised *via* general procedure C. Isolated as a single diastereoisomer as a white solid (122 mg, 54 %); m.p. 135-137 °C; ¹H NMR (CDCl₃, 500 MHz) δ 1.10 (3H, t, *J* = 7.4, CH₃), 1.83 (1H, apt. d quint, *J* = 14.8, 7.5, CHHCH₃), 2.13 (1H, dqd, *J* = 15.1, 7.5, 4.8, CHHCH₃), 3.32 (1H, ddd, *J* = 8.4, 6.7, 4.7, CH₂Et), (1H, dd, *J* = 5.3, 6.7, CHNO₂), 5.61 (1H, d, *J* = 5.3, CHNAr), 6.80 (2H, m, ArH), 7.24 (4H, ArH), 7.35 (3H, m, ArH). All other data in agreement with literature.⁹³

4.7 Synthesis of Ligands

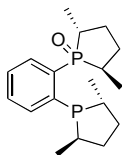
2-(diphenylphosphino)-L-Tle-L-Tyr(OBn)-NEt₂ - 229⁶¹



To a solution of Boc-L-Tyr(OBn)-OH (1.59 g, 4.28 mmol) in DCM (25 mL) was added EDC.HCl (0.82 g, 4.28 mmol), HOBT.H₂O (0.66 g, 4.28 mmol) and diethylamine (0.93 mL, 8.98 mmol). The resulting solution was allowed to stir at rt for 4 h. The reaction was quenched by the addition of citric acid soln. (10 % wt., 20 mL), the organic layer washed with citric acid soln. (2 × 20 mL), sat. NaHCO₃ soln. (20 mL), brine (20 mL), dried (MgSO₄) and concentrated to afford a yellow oil (1.40 g). TFA (1.22 mL, 16.41 mmol) was added to a

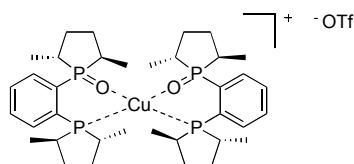
solution of Boc-L-Tyr(OBn)NEt₂ (1.40 g, 3.28 mmol) in DCM (10 mL) at 0 °C, and allowed to stir for 3 h. The reaction was quenched by the addition of 6N KOH soln. until pH >10, and the organic layer separated, dried (MgSO₄) and concentrated to afford a yellow oil (0.91 g, 2.78 mmol). To a solution of NH₂-L-Tyr(OBn)-NEt₂ (0.91 g, 2.78 mmol) in DCM (25 mL) was added EDC.HCl (0.59 g, 3.06 mmol), HOBT.H₂O (0.47 g, 3.06 mmol) and Boc-L-Tle-OH (0.643 g, 2.78 mmol). The resulting solution was allowed to stir at rt for 4 h. The reaction was quenched by the addition of citric acid soln. (10 % wt., 20 mL), the organic layer washed with citric acid soln. (2 × 20 mL), sat. NaHCO₃ soln. (20 mL), brine (20 mL), dried (MgSO₄) and concentrated to afford a yellow oil (1.17 g). TFA (1.22 mL, 16.41 mmol) was added to a solution of Boc-L-Tle-L-Tyr(OBn)NEt₂ (1.17 g, 2.17 mmol) in DCM (10 mL) at 0 °C, and allowed to stir for 3 h. The reaction was quenched by the addition of 6N KOH soln. until pH >10, and the organic layer separated, dried (MgSO₄) and concentrated to afford a yellow oil (0.55 g, 1.29 mmol). To a solution of NH₂-L-Tle-L-Tyr(OBn)-NEt₂ (0.55 g, 1.29 mmol) in DCM (5 mL) was added 2-(diphenylphosphino)benzaldehyde (0.38 g, 1.292 mmol) and MgSO₄ (0.80 g) and the reaction allowed to stir for 48 h at rt. After this time the reaction was filtered through celite, washed with DCM and concentrated to afford a brown oil, which was purified by flash chromatography to yield a cream foam (0.57 g, 19 %): ¹H NMR (400 MHz, CDCl₃) δ 0.69 (9H, s, (CH₃)₃), 0.91-0.98 (6H, m, N(CH₂CH₃)₂), 2.92-3.10 (5H, m, N(CH₂CH₃)₂ and CHCHHAr), 3.36 (1H, s, NCHCO), 3.46 (1H, dd, *J* = 14.0, 7.2, CHCHHAr), 5.04 (2H, s, ArCH₂O), 5.06-5.12 (1H, m, NCHCO), 6.85-6.90 (3H, m, CHAr), 7.16-7.22 (4H, m, CHAr), 7.26-7.46 (15H, m, CHAr), 7.76 (1H, d, *J* = 8.8, CHAr), 7.98 (1H, ddd, *J* = 7.2, 3.6, 1.2, CHAr), 8.62 (1H, d, *J* = 4.4, N=CH). All other data were in accord with literature.⁶¹

(2*R*,5*R*)-1-{2[(2*R*,5*R*)2,5-Dimethylphospholan-1-yl]phenyl}-2,5-dimethylphospholane 1-oxide(BozPHOS)¹²⁰



To a solution of (*R,R*)-(Me)-DUPHOS (500 mg, 1.63 mmol) in THF (16 mL) was added $\text{BH}_3\cdot\text{Me}_2\text{S}$ (10 M, 180 mL, 1.80 mmol) at 0 °C. The mixture was stirred for 45 min at this temperature. H_2O_2 (30% (v/v), 2.0 mL, 19.6 mmol) was added and the mixture stirred for 25 min before being quenched with sat. Na_2SO_3 (2 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3x5 mL), dried (Na_2SO_4), filtered and solvent removed *in vacuo*. The crude product was immediately dissolved in benzene (16 mL) and treated with DABCO (275 mg, 2.45 mmol) at 50 °C. The reaction mixture was stirred for a further 5 h at 50 °C, the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, 5% MeOH/EtOAc) to provide the title compound as a white solid (486 mg, 92%): m.p. 120-121 °C; $[\alpha]_{\text{D}}^{26} +129.6$ (c 0.55, DCM); ^1H NMR (C_6D_6) δ 0.86 (3H, d, $J = 17.2, 7.6$, CH_3), 1.01 (1H, m, CH_2), 1.08 (3H, apt. t, $J = 16.0$, CH_3), 1.24 (8H, m, 2 x $\text{CH}_3 + \text{CH}_2$), 1.73 (2H, m, CH_2), 1.96 (4H, m, CH_2), 2.51 (1H, m, CH), 2.68 (1H, m, CH_2), 2.71 (1H, m, CH_2), 7.01 (1H, m, ArH), 7.10 (1H, m, ArH), 7.33 (1H, m, ArH), 7.49 (1H, m, ArH). All other data in agreement with literature.¹²⁰

Copper(+)-bis[(2*R*,5*R*)-1-[2-[(2*R*,5*R*)-2,5-dimethyl-1-phospholanyl-P]phenyl]-2,5-dimethylphospholane 1-(oxide-O)]-, (T-4)-, 1,1,1-trifluoromethanesulfonate (1:1) - 223¹²¹



BozPHOS (486 mg, 1.52 mmol) and (CuOTf)₂.PhMe (194 mg, 0.381 mmol) were dissolved in anhydrous MeCN (10 mL) to provide a dark green solution. Stirring for 1 h at room temperature resulted in an emerald green solution, the solvent was removed *in vacuo* to leave a green paste. Purification by column chromatography (silica, 5% MeOH/DCM) provided the title compound as a pale yellow solid (401 mg, 56%): m.p. 197-199 °C; $[\alpha]_D^{28} +7.07$ (c 0.64, CHCl₃); ¹H NMR (CD₂Cl₂) δ (6H, d, *J* = 5.2, 2 x CH₃), 0.97 (6H, d, *J* = 5.2, 2 x CH₃), 1.25 (3H, d, *J* = 7.2, CH₃), 1.28 (3H, d, *J* = 5.2, CH₃), 1.41-1.83 (22H, m, CH₂ + CH), 2.89 (2H, m, CH₂), 7.42 (2H, m, ArH), 7.68 (4H, m, ArH), 7.79 (2H, m, ArH). All other data in agreement with literature.¹²¹

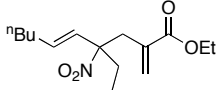
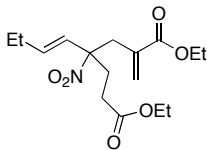
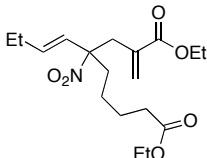
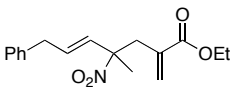
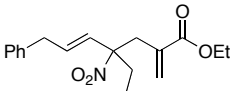
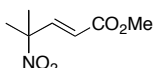
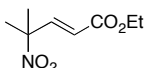
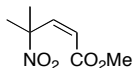
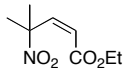
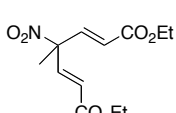
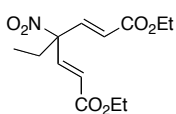
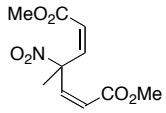
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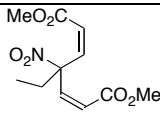
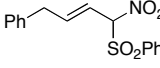
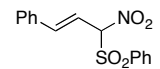
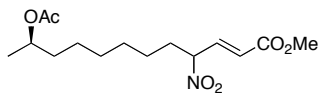
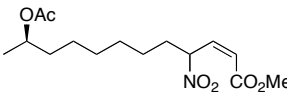
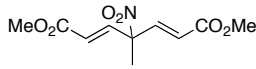
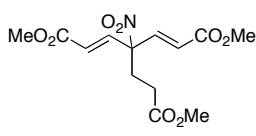
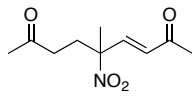
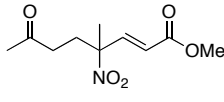
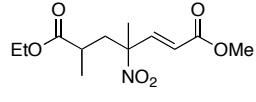
Appendices

Appendix A - *J*-Values For Non-Conjugated Nitro-Alkenes

The following compounds have been used to analyse the coupling constants of both *cis*- and *trans*- allylic nitro compounds. The *J* value is taken directly from the journal data.

Entry	Reference	Structure	<i>J</i> value / Hz
1	1		10.1
2	1		10.2
3	2		15.6
4	2		10.6
5	2		10.2
6	2		10.0
7	2		10.4
8	3		15.7

9	3		16.1
10	3		16.1
11	3		16.2
12	3		15.7
13	3		16.0
14	4		16.0
15	4		16.2
16	4		12.6
17	4		12.4
18	4		16.0
19	4		16.2
20	4		12.2

21	4		12.1
22	5		15.5
23	5		15.3
24	6		16.0
25	6		12.0
26	7		16.0
27	7		16.1
28	7		16.1
29	7		16.4
30	7		16.0

Ref 1: Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X. *Org. Lett.* **2007**, *9*, 4495;

Ref 2: Alameda-Angulo, C.; Quiclet-Sire, B.; Schmidt, E.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3489;

Ref 3: Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron*, **2004**, *60*, 4995;

Ref 4: Michaud, D.; Hamelin, J.; Texier-Boullet, F. *Tetrahedron*, **2003**, *59*, 3323;

Ref 5: Wade, P. A.; Murray, J. K.; Shah-Patel, S.; Palfey, B. A.; Carroll, P. J. *J. Org. Chem.* **2000**, *65*, 7723;

Ref 6: Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron*, **1999**, *55*, 5177;

Ref 7: Anderson, D. A.; Hwu, J. R. *J. Org. Chem.* **1990**, *55*, 511.

Appendix B - J-Values For Selected Nitroamines

The following table lists the structures and a selection of relevant coupling constants of the β -nitroamines and amides synthesised during the period of these studies, along with pertinent examples from Dr G. Stepney's work. Relative diastereochemistry was assigned by either crystal structures, or in the cases where crystals were of insufficient quality to permit X-ray crystallography, by analogy with other examples synthesised using the same method. The coupling constants are reported as observed, and have not been averaged. Heading J_a^1 refers to the coupling constant between proton a and b (**Figure 27**) in the signal for proton a. Heading J_b^1 refers to the same coupling constant but in the signal for proton b. Likewise heading J_b^2 refers to the coupling constant between proton b and c in the signal for proton b and J_c^1 refers to the same coupling constant in proton c. All coupling constants are reported in Hz.

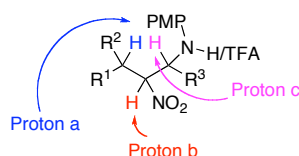
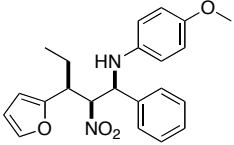
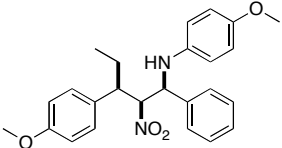
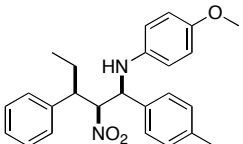
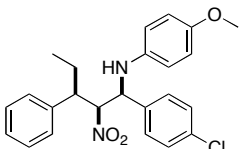
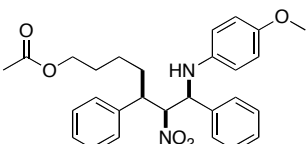
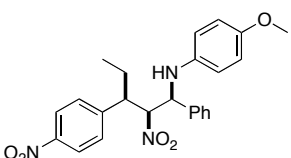
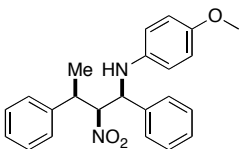
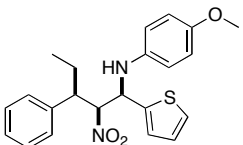
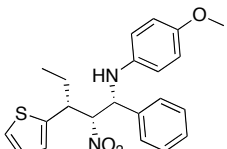
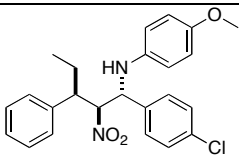
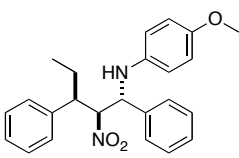
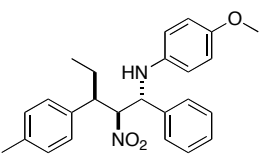
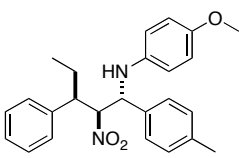
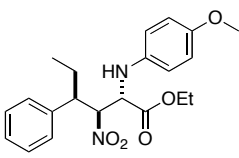
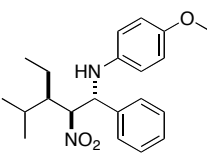
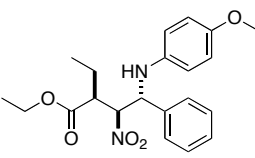
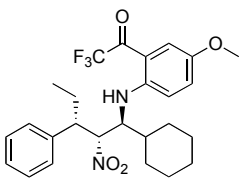
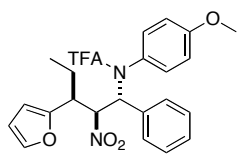
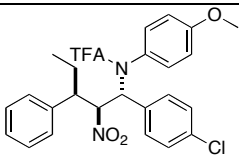
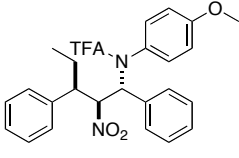
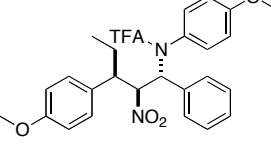
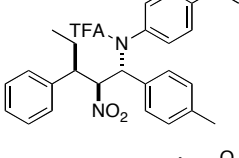
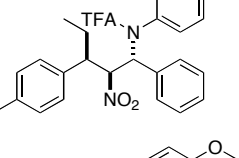
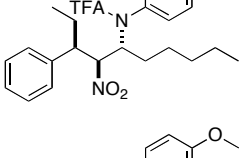
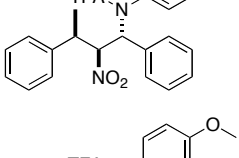
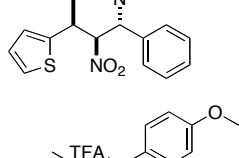
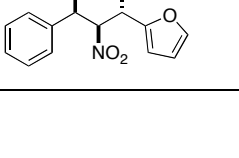


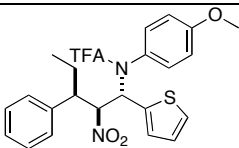
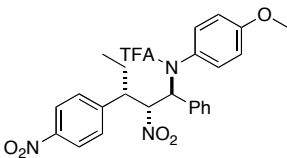
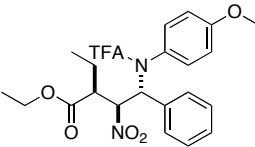
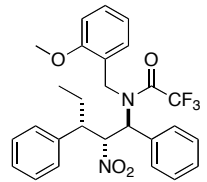
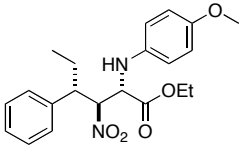
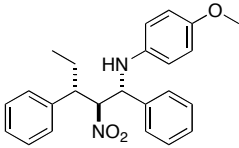
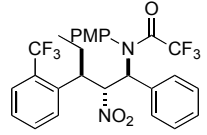
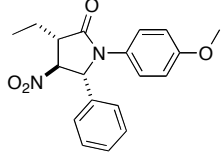
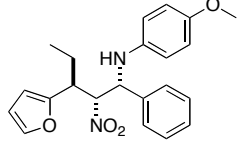
Figure 27: Diagram of protons used in the coupling constant tabulation

Entry	Structure	X-Ray	J_a^1	J_b^1	J_b^2	J_c^1
1		yes	11.3	11.1	3.6	3.5
2		no	11.3	11.1	3.6	3.5

3		yes	11.0	10.6	4.0	4.0
4		yes	11.6	10.8	3.2	3.2
5		yes	11.4	11.1	3.6	3.2
6		no	11.3	11.1	3.5	3.4
7		no	11.2	11.2	3.6	3.6
8		no	11.1	10.9	4.0	4.0
9		no	10.9	10.9	3.8	3.7
10		no	11.3	10.9	3.7	3.5
11		no	11.0	11.0	3.6	3.5

12		no	10.9	10.6	4.1	4.1
13		no	10.8	10.8	4.1	4.0
14		no	10.8	10.6	4.1	not seen
15		no	10.7	10.6	4.2	4.6
16		yes	11.6	11.6	2.4	2.8
17		no	11.4	11.0	3.0	4.8
18		no	10.5	10.5	5.0	5.0
19		no	4.1	4.7	9.7	10.4
20		yes	3.2	3.8	11.4	11.7

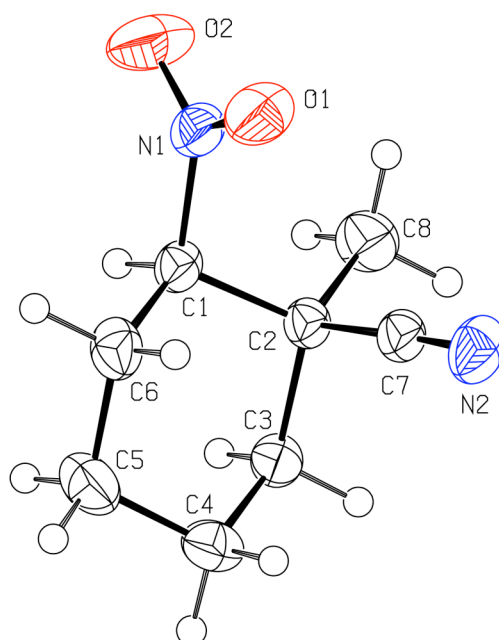
21		no	5.3	5.4	10.2	10.1
22		yes	4.8	4.9	10.5	10.1
23		no	4.8	4.9	10.4	m
24		no	4.8	4.9	10.5	10.5
25		no	4.6	4.8	10.4	10.4
26		no	4.0	3.9	10.2	m
27		no	4.3	4.4	10.9	10.7
28		yes	3.6	3.6	11.0	11.0
29		yes	8.5	8.1	8.1	11.0

30		no	7.0	7.2	8.5	8.5
31		no	4.3	4.5	10.1	9.9
32		no	3.6	m	m	10.6
33		yes	4.6	4.8	10.5	10.6
34		no	8.7	8.6	5.7	5.7
35		no	7.4	7.2	7.2	5.8
36		yes	9.1	8.7	8.7	8.7
37		yes	6.7	6.7	5.3	5.3
38		no	5.3	5.7	8.0	7.9

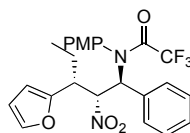
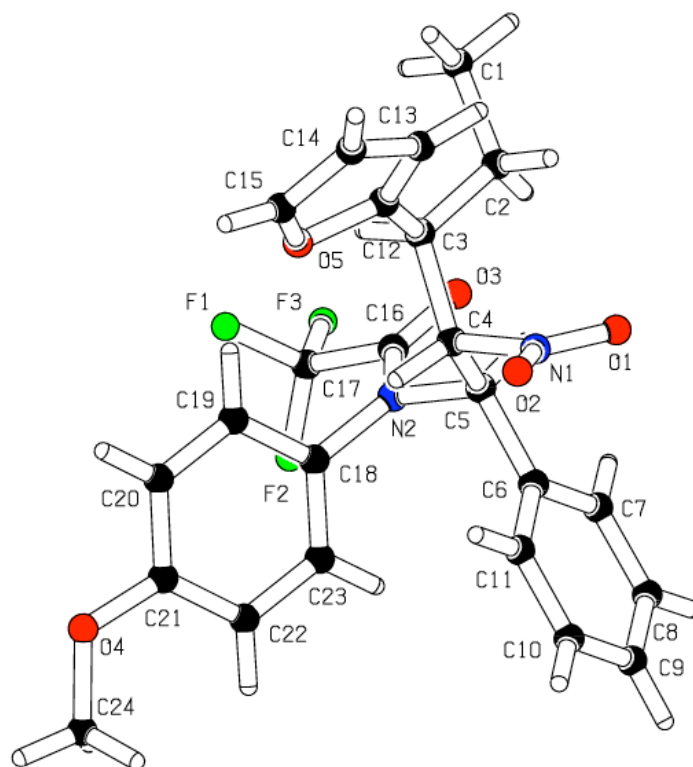
Appendix C - X-Ray Crystallographic Data

All crystallographic data was collected by Prof. Alexander J. Blake and Dr. William Lewis (University of Nottingham) and Prof. D. Tocher (University College London). The analyses below have been deposited in the Cambridge Crystallographic Database.

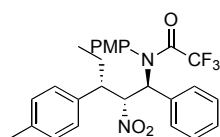
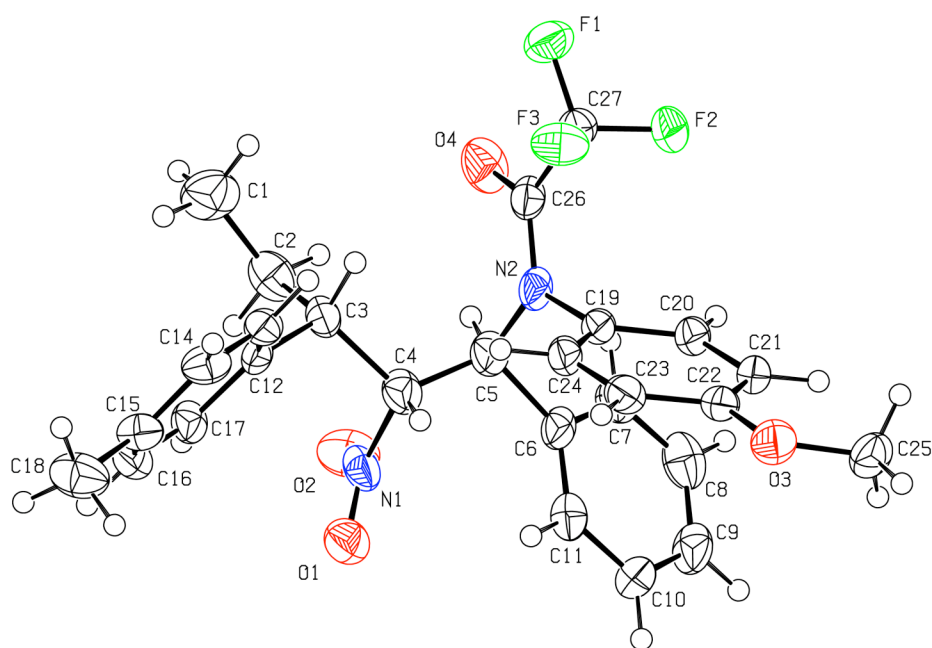
1-Methyl-2-nitro-cyclohexanecarbonitrile



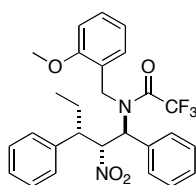
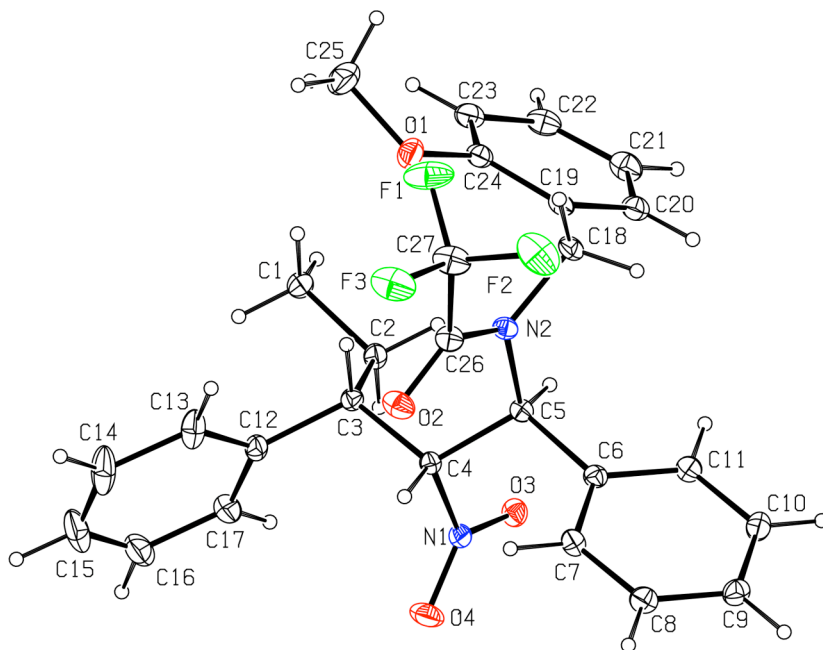
2,2,2-Trifluoro-*N*-((1*S*,2*R*,3*R*)-3-furan-2-yl-2-nitro-1-phenyl-pentyl)-*N*-(4-methoxy-phenyl)-acetamide



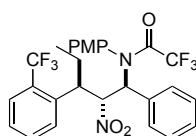
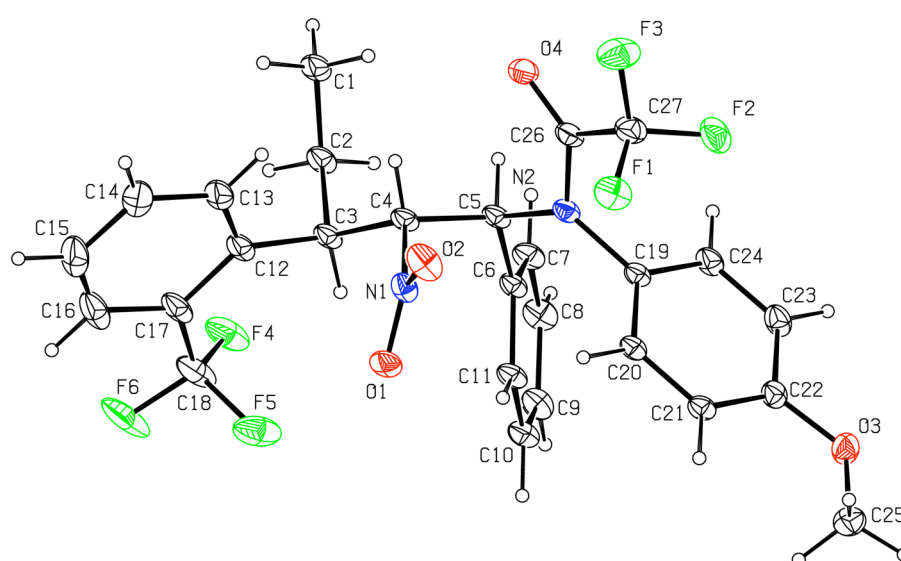
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*S*,2*R*,3*S*)-2-nitro-1-phenyl-3-*p*-tolyl-pentyl)-acetamide



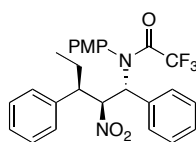
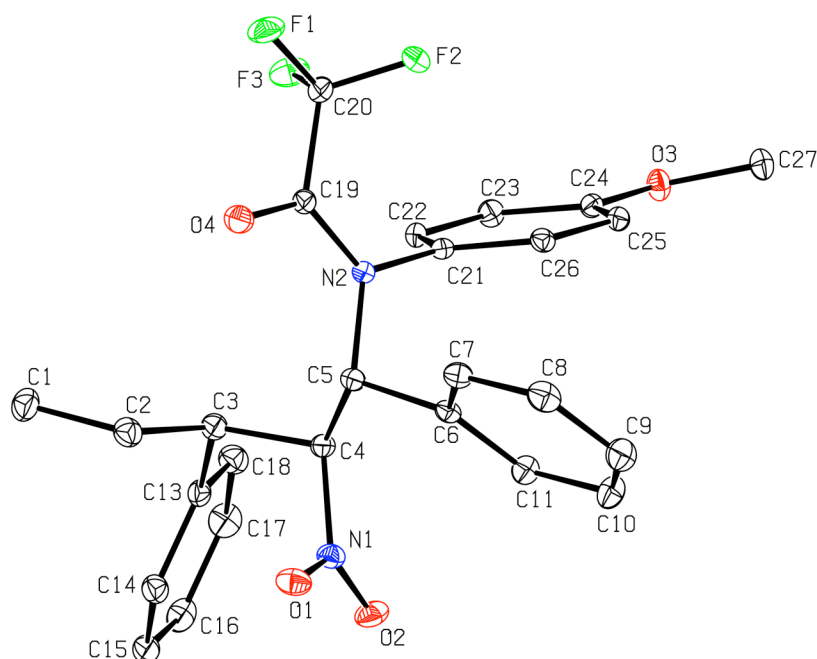
(±)-2,2,2-Trifluoro-*N*-(2-Methoxy-benzyl)-*N*-((1*R,2*S**,3*R**)-2-nitro-1,3-diphenyl-pentyl)-acetamide**



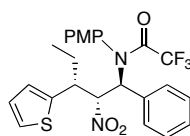
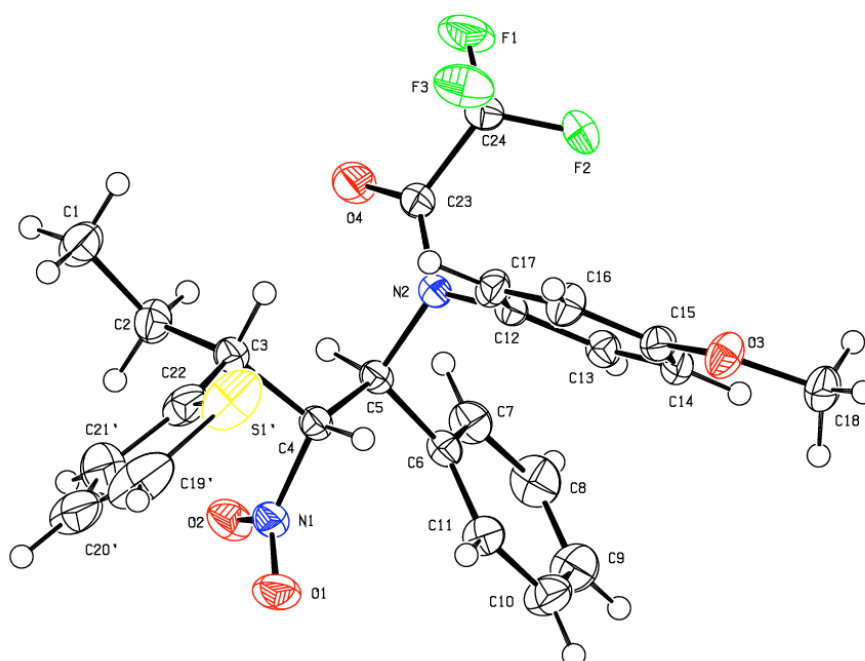
(±)-2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-[(1*S,2*R**,3*R**)-2-nitro-1-phenyl-3-(2-trifluoromethyl-phenyl)-pentyl]-acetamide**



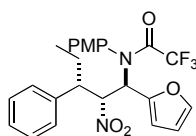
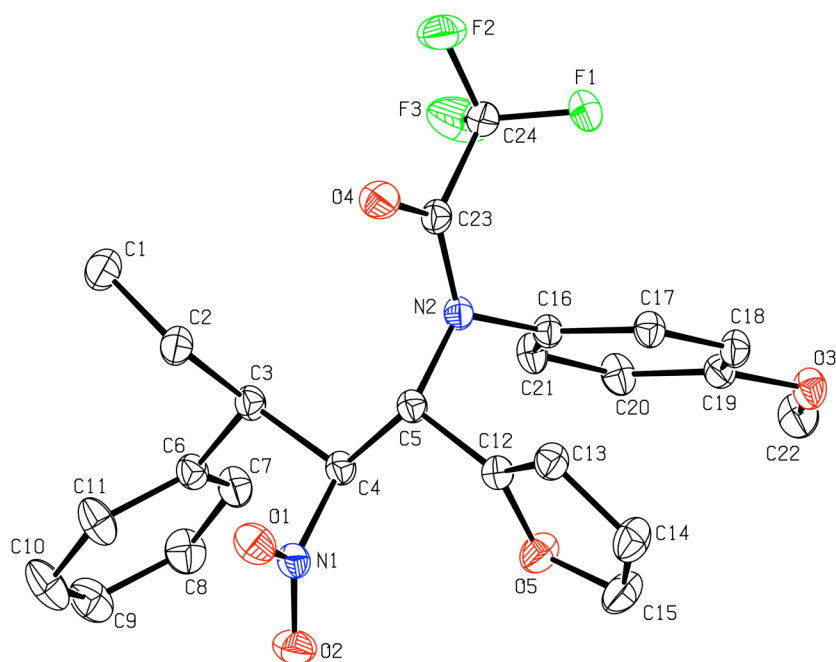
2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*R*,2*S*,3*R*)-2-nitro-1,3-diphenyl-pentyl)-acetamide

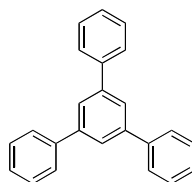
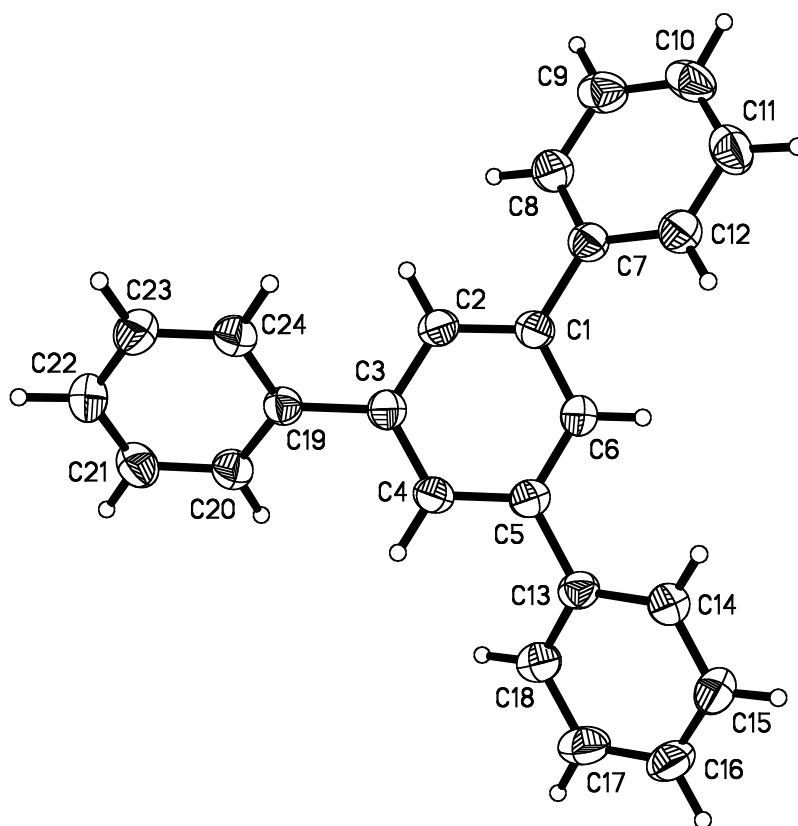


2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-*N*-((1*S*,2*R*,3*R*)-2-nitro-1-phenyl-3-thiophen-2-yl-pentyl)-acetamide



(±)-2,2,2-Trifluoro-*N*-((1*S*,2*R*,3*S*)-1-furan-2-yl-2-nitro-3-phenyl-pentyl)-*N*-(4-methoxy-phenyl)-acetamide



1,3,5-Triphenylbenzene

Appendix D - Abbreviations

δ	chemical shift
Å	Angstrom
Ac	acetyl
acac	2,4-pentanedione
Ar	aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
[bmim]	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOX	<i>bis</i> -oxazoline
ⁿ Bu	<i>normal</i> -butyl
^t Bu	<i>tert</i> -butyl
C	Celsius
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CI	chemical ionisation
Cy	cyclohexyl
dr	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
<i>de</i>	diastereomeric excess
DEAD	diethyl azodicarboxylate
deg	degraded
DIPEA	<i>diisopropyl</i> ethylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DME	dimethoxyethane

DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E	electrophile
<i>ee</i>	enantiomeric excess
EI	electron impact
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
h	hour
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IPA	<i>isopropanol</i>
IR	infrared spectroscopy
<i>J</i>	coupling constant
K	Kelvin
kcal	kilocalorie
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
<i>m</i>	<i>meta</i>
Me	methyl
(Me)-DUPHOS	2,2',5,5'-Tetramethyl-1,1'-(<i>o</i> -phenylene)diphospholane
min	minute
MMPP	magnesium bis(monoperoxyphthalate) hexahydrate

m.p.	melting point
MS	molecular sieves
Ms	mesyl
NMR	nuclear magnetic resonance
Nu	nucleophile
<i>o</i>	<i>ortho</i>
OMB	<i>ortho</i> -methoxy benzyl
OMP	<i>ortho</i> -methoxy phenyl
OTf	triflate
<i>p</i>	<i>para</i>
PG	protecting group
Ph	phenyl
ⁿ Pn	<i>normal</i> -pentyl
PMB	<i>para</i> -methoxy benzyl
PMP	<i>para</i> -methoxy phenyl
ppm	parts per million
ⁱ Pr	<i>iso</i> -propyl
RAMP	(+)-(R)-1-amino-2-(methoxymethyl)pyrrolidine
Ra-Ni	Raney [®] nickel
R _f	retention factor
rt	room temperature
s	second
s.m.	starting material
TADDOL	2-Phenyl- $\alpha,\alpha',\alpha',\alpha'$ -tetraphenyldioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBME	<i>tert</i> -butylmethyl ether
temp	temperature
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anydride
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
Tle	<i>tert</i> -leucine
TMS	trimethylsilyl
Ts	tosyl
Tyr	tyrosine
18-C-6	18-crown-6

Appendix E - References

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